STUDY ON RE-ESTABLISHMENT OF OVULATION AFTER TERMINATION OF SEX-STEROIDAL TREATMENT
—COMPARSED WITH RE-APPEARANCE OF OVULATION AFTER ABORTION AND PREMATURE DELIVERY—

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ABSTRACT

Analysis of basal body temperature patterns (BBT) after continuous treatment with sex-steroids reveals that an extremely high percentage of subjects experience a delayed re-establishment of ovulation in the post treatment cycles, whereas the delayed re-appearance of ovulation is also observed with a high percentage in the recovery process of hypothalamic, pituitary and ovarian functions after abortion or premature delivery. It is, therefore, suggested that these endocrine functions are affected to a certain extent by the use of sex-steroids or by the gestation.

On BBT
1. In the first cycle after the termination of sex-steroidal treatment, 76% of the 6-cycle (treatment) group, 92.3% of the 12-cycle group and 87.5% of the 18–20-cycle group showed a prolonged menstrual cycle.
2. Noticeable characteristics in (1.) above, were a lengthened low phase and a shortened high phase. This low phase correlated with treated durations.
3. The onset date of first menstruation in the post gestational period was delayed in the premature delivery group, and the noticeable characteristics were a lengthened low phase and a shortened high phase. This low phase correlated with gestational durations before abortion or premature delivery.

On LH-RH test
1. LH response to LH-RH was detected from 2nd week (counting from 1st day of withdrawal bleeding after treatment) in 6- and 12-cycle groups, and from 3rd week in the 18–20-cycle group.
2. FSH response to LH-RH in 12- and 18–20-cycle groups showed a
remarkably high level from 1st week, whereas its response in the 6-cycle group registered a slightly high level.

3. In the 6-cycle group, the larger the amount administered, the longer delayed the recovery in LH response to LH-RH and the more remarkable the increase of FSH response.

4. The recovery in LH response to LH-RH in the premature delivery group was delayed compared with that in the abortion groups, and its response was noticed in the 4th week after premature delivery.

5. FSH response to LH-RH weekly exceeded a higher level in the premature delivery group than in the abortion groups. As ovulation approached, FSH recovered a normal preovulatory stage level.

INTRODUCTION

Analysis of basal body temperature patterns (BBT) after continuous treatment with sex-steroids reveals an extremely high percentage of subjects experience a delayed re-establishment of ovulation in th post treatment cycles (Fig. 1), whereas the delayed re-appearance of ovulation is also observed with a high percentage in the recovery process of hypothalamic, pituitary and ovarian functions after abortion or premature delivery. It is, therefore, suggested that these endocrine functions are affected to a certain extent by the use of sex-steroids or by the gestation.

For both the establishment of sex-steroidal contraceptives treatment conditions and its administration, it is vitally important to understand in advance how hypothalamic, pituitary and ovarian functions are affected by the estrogen and progesterone types as well as by the duration of treatment, and also to compare the result with the endocrine function on the recovery process of ovulation.

![Fig. 1 BBT after termination of sex-steroidal treatment length of pre-treatment menstrual cycle 28 days. Ov.: day of presumable ovulation.](image-url)
after abortion or premature delivery.

The study was made by Flowers, et al., Nunokawa, et al. and Ikeda on the recovery of pituitary function after termination of treatment with sex-steroids. However, no one has yet reported on the re-establishment of ovulation after termination of treatment through such investigations as BBT and LH-RH test in categorizing by sex-steroids composition (type of oral contraceptive) and duration of treatment. Moreover, the re-appearance of ovulation in puerperium was studied by Lyon, Perez and Ko. But, the endocrine functions in post abortion or post premature delivery are only indistinctly comprehensive because of difficulty in the long-term follow through required.

In analyzing the recovery process after termination of treatment with sex-steroids and endocrinologically investigating the re-establishment of ovulation after abortion or premature delivery through the preceding methods, this author, based on these data, has sought to establish a clinical guide to treatment conditions and administration of sex-steroids as anti-ovulation compounds.

MATERIALS AND METHODS

1. Subjects

Seventy-nine women were administered with sex-steroidal oral contraceptives. The administration periods were classified into the following three groups: (A) 6-cycle treatment group...26 cases, (B) 12-cycle treatment group...14 cases, (C) 18-20-cycle treatment group...12 cases.

Three patients who had dysmenorrhea needed a pseudopregnancy therapy.

Thirteen patients who experienced either abortion or premature delivery from 10 through 34 weeks of gestation were classified into the following three groups: (a) 10-13 weeks gestational abortion group...4 cases, (b) 19-21 weeks gestational abortion group...4 cases, (c) 28-34 weeks gestational premature delivery group...5 cases.

All subjects were from the gynecological clinic of Keio University Hospital. They had normal menstrual cycles (28 to 35 days) and their age range was from 19 to 42 years.

2. Methods

(a) Mode of treatment with sex-steroids

As for oral contraceptives, one tablet (estrogen compound + progesterone compound (Table 1) was taken from day 5 (the fifth day of the cycle counting from the first day of the menstrual flow), daily, for 20 days, which was considered as one treatment cycle. This cycle was repeated (combination method).
Table 1
Oral contraceptive compounds

<table>
<thead>
<tr>
<th></th>
<th>Estrogen compound</th>
<th>+Progesterone compound</th>
<th>Trade name</th>
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</thead>
<tbody>
<tr>
<td>Combination method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tablet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mestranol 0.1 mg</td>
<td>nomorethisterone acetate 2.0 mg</td>
<td>Sophia C</td>
<td></td>
</tr>
<tr>
<td>mestranol 0.05 mg</td>
<td>nomorethisterone 1.0 mg</td>
<td>Norlutent D1</td>
<td></td>
</tr>
<tr>
<td>mestranol 0.15 mg</td>
<td>lynestrenol 5.0 mg</td>
<td>Lyndiol 5</td>
<td></td>
</tr>
<tr>
<td>mestranol 0.075 mg</td>
<td>lynestrenol 2.5 mg</td>
<td>Lyndiol 2.5</td>
<td></td>
</tr>
<tr>
<td>Pseudopregnancy therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1 tablet)</td>
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<td></td>
<td></td>
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<tr>
<td>mestranol 0.075 mg</td>
<td>lynestrenol 2.5 mg</td>
<td>Lyndiol 2.5</td>
<td></td>
</tr>
<tr>
<td>mestranol 0.1 mg</td>
<td>nomorethisterone 2.0 mg</td>
<td>Sophia C</td>
<td></td>
</tr>
<tr>
<td>mestranol 0.08 mg</td>
<td>chlormadinone acetate 2.0 mg</td>
<td>Lutral S</td>
<td></td>
</tr>
</tbody>
</table>

The treatment cycles were mainly: (A) 6-cycle, (B) 12-cycle, and (C) 18–20-cycle, but partly included such varied treatment as 3-cycle (the shortest) to 63-cycle (the longest).

As for pseudopregnancy therapy, one tablet (mestranol + progesterone compound) (Table 1) was taken daily from day 5 for six months continuously.

(b) Interpretation of BBT
Both BBTs before and after treatment with sex-steroids and BBTs before and after gestation were investigated. The presence of ovulation was presumed by reference to BBT in which the high phase of more than 5 days preceded the uterine bleeding.

(c) LH-RH test, serum LH and FSH levels measurement
LH-RH tests on 38 subjects with sex-steroidal treatment were performed every week counting from the first day of the withdrawal bleeding after termination of treatment. Also, the same tests on 10 subjects who experienced either abortion or premature delivery were performed every week in the post gestational period.

In regard to the method of LH-RH test, 100 μg of synthetic LH-RH was administered intramuscularly to each subject. Serum LH and FSH levels were determined by RIA immediately before, and 30 and 60 minutes after the injection (Kurokawa).7

H-LH and H-FSH kits (supplied by Daiichi Radioisotope Laboratories, Ltd.) were used in the LH and FSH assay (Nakamura, et al.).8

(d) Statistical analysis followed Student’s t-test.
RESULTS

1. Menstrual cycles and BBTs before and after treatment with sex-steroids, and before and after gestation

Table 2 demonstrates the investigation made on the first cycle after termination of treatment with different types of sex-steroids and also for varying treated durations. The pre-treatment menstrual cycle was 29.0 ± 0.3 days.

In the analysis of all results obtained, 76% of the 6-cycle treatment group, 92.3% of the 12-cycle group and 87.5% of the 18-20-cycle group showed a prolonged menstrual cycle in the first cycle after termination of treatment (except for 2 subjects who became amenorrhoea due to pregnancy immediately after treatment). On the other hand, no notable correlation was detected between the amounts administered per day (the types of sex-steroids) and the prolonged post treatment cycle. This prolongation, when reviewed in BBT analysis, revealed that a lengthened low phase and a shortened high phase were noticeable characteristics: namely, in making studies on BBTs in the first cycle after termination of treatment, presumable ovulation dates were on day 22.9 ± 1.0 in the 6-cycle treatment group, on day 24.3 ± 1.2 in the 12-cycle group and on day 26.8 ± 1.4 in the 18-20-cycle group (Table 2). Therefore, the longer the sex-steroidal administration, the longer delayed the re-establishment of ovulation. No notable correlation was detected between the treatment durations and the shortened high phase. However, it was impossible to presume ovulation from three of the seven subjects in the 18-20-cycle treatment group administered with tablets (mestranol 0.1 mg + norethisterone 2.0 mg/tablet). In the remaining 4 subjects in which an ovulation was confirmed, the durations of high phase were 10.3 ± 1.3 days and they were significantly shorter than the periods in the pre-treatment cycle.

Then, by observing 9 subjects in the second cycle after termination of treatment, it was noticed that BBTs of 3 subjects (33.3%) in the 6-cycle treatment group and of 2 subjects (22.2%) in the 18-20-cycle group had recovered a normal pattern.

Additionally, the subjects who demonstrated an irregular pattern on BBT and developed a break through bleeding without ovulation in the first cycle were one subject each in the 6-cycle and the 12-cycle treatment groups and 3 subjects in the 18-20-cycle group. However, no subjects with amenorrhoea were found after termination of treatment. Continued observation of these irregular patterns revealed the existence of the biphasic patterns that involved a delayed ovulation in the second cycle after termination of treatment.

Table 3 depicts results of the investigation made in the first cycle after
<table>
<thead>
<tr>
<th>sex-steroids/tablet</th>
<th>cases</th>
<th>duration of treatment</th>
<th>duration of treatment</th>
<th>duration of treatment</th>
<th>duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3 cycles</td>
<td>6 cycles</td>
<td>12 cycles</td>
<td>18–20 cycles</td>
</tr>
<tr>
<td></td>
<td></td>
<td>onset of ovulation</td>
<td>duration of high phase</td>
<td>onset of ovulation</td>
<td>duration of high phase</td>
</tr>
<tr>
<td>mestranol 0.075 mg</td>
<td>23</td>
<td>19.0±1.0 th day</td>
<td>12.5±0.8 days</td>
<td>24.1±1.8</td>
<td>12.8±0.5</td>
</tr>
<tr>
<td>+ lynestrenol 2.5 mg</td>
<td></td>
<td></td>
<td>(pregnancy 1 case)</td>
<td>(anovulation 1 case)</td>
<td></td>
</tr>
<tr>
<td>(Lyndiol 2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mestranol 0.15 mg</td>
<td>7</td>
<td>20.5±2.5</td>
<td>10.0±1.0</td>
<td>19.0±1.0</td>
<td>11.0±1.0</td>
</tr>
<tr>
<td>+ lynestrenol 5.0 mg</td>
<td></td>
<td></td>
<td>(anovulation 1 case)</td>
<td>(anovulation 1 case)</td>
<td></td>
</tr>
<tr>
<td>(Lyndiol 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mestranol 0.05 mg</td>
<td>8</td>
<td>17.0±1.0</td>
<td>11.0±1.5</td>
<td>20.0±2.4</td>
<td>12.4±0.5</td>
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<tr>
<td>+ norethisterone 1.0 mg</td>
<td></td>
<td></td>
<td>(Norlutren D₁)</td>
<td>(anovulation 1 case)</td>
<td></td>
</tr>
<tr>
<td>(Sophia-C)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mestranol 0.1 mg</td>
<td>25</td>
<td></td>
<td></td>
<td>24.8±1.4</td>
<td>11.7±0.8</td>
</tr>
<tr>
<td>+ norethisterone 2.0 mg</td>
<td></td>
<td></td>
<td></td>
<td>(anovulation 1 case)</td>
<td>(anovulation 1 case)</td>
</tr>
<tr>
<td>(Sophia-C)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ethinylestradiol 0.05 mg</td>
<td>5</td>
<td>19.0±1.5</td>
<td>12.7±0.7</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>+ norethindrone acetate 4.0 mg</td>
<td></td>
<td>(Anovular)</td>
<td></td>
<td>(pregnancy 1 case)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>18.8±0.7</td>
<td>11.9±0.5</td>
<td>22.9±1.0</td>
<td>12.0±0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(pregnancy 1 case)</td>
<td>(anovulation 1 case)</td>
<td>(anovulation 1 case)</td>
<td>(anovulation 1 case)</td>
</tr>
</tbody>
</table>

Means ± S.E., length of pre-treatment cycle 29.0 ± 0.3 days
First Ovulation After Sex-steroidal Treatment

Table 3
Onset of ovulation & duration of high phase in the cycle after abortion & premature delivery

<table>
<thead>
<tr>
<th>duration of gestation</th>
<th>cases</th>
<th>menstrual cycle in post gestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>the first cycle</td>
</tr>
<tr>
<td></td>
<td></td>
<td>onset of ovulation</td>
</tr>
<tr>
<td>10–13 weeks</td>
<td>4</td>
<td>17.0±0.4 th day 12.0±0.7 days</td>
</tr>
<tr>
<td>19–21 weeks</td>
<td>4</td>
<td>31.0±1.8 10.3±1.2</td>
</tr>
<tr>
<td>28–34 weeks</td>
<td>5</td>
<td>38.0±1.5 (anovulation 2 cases)</td>
</tr>
</tbody>
</table>

mean ± S.E., length of pre-gestational menstrual cycle 27.7 ± 0.4 days

abortion and premature delivery. The pregestational menstrual cycle was 27.7 ± 0.4 days. The average onset date of the first menstruation was on day 40.5 ± 2.2 after these gestations. The first menstrual cycle in the 10–13 weeks gestational abortion group was a 29.0 ± 0.4 day pattern, which was not prolonged. But the first menstrual cycles in the 19–21 weeks abortion group and the 28–34 weeks premature delivery group both indicated prolonged cycles. The cycle in the former group was a 41.3 ± 1.3 day pattern, and in the latter group was a 49.2 ± 2.1 day pattern. When reviewed in BBT analysis, this prolongation revealed that a lengthened low phase and a shortened high phase were noticeable characteristics. Namely, presumable ovulation dates in the first menstrual cycle were on day 17.0 ± 0.4 in the 10–13 weeks gestational abortion group, on day 31.0 ± 1.8 in the 19–21 weeks abortion group and on day 38.0 ± 1.5 in the 28–34 weeks premature delivery group. This result was similar to the BBT after termination of treatment with sex-steroids. In the premature delivery group, 2 subjects indicated no clear expected ovulation date. Accordingly, the longer the gestational period, the longer delayed the re-establishment of ovulation. On the other hand, the duration of the high phase was 11.0 ± 0.6 days on average for the subjects in which it was possible to confirm ovulation. The duration in the premature delivery group was significantly shorter than that in the pre-gestational period.

Then, by observing BBTs in the second cycle after the gestations of 3 subjects in the 10–13 weeks gestational abortion group and of 4 subjects in the 28–34 weeks premature delivery group, it was noticed that BBTs in the former
group had recovered a normal pattern, while the cycle in the latter group was a 27.0 ± 1.0 day pattern with a presumable ovulation date on day 15.5 ± 0.5 and a high phase for 12.0 ± 0.7 days. However, no subjects with irregular patterns on BBTs were found.

2. LH-RH test, serum LH and FSH levels both after treatment with sex-steroids and after gestation

(a) Cases treated with tablets (mestranol 0.1 mg + norethisterone 2.0 mg/tablet) (Figs. 2 & 3)

Fig. 2 depicts studies on LH-RH tests conducted every week counting from the first day of the withdrawal bleeding in the first cycle after termination of treatment. LH in the first week was shown only in the 6-cycle treatment group.
and demonstrated a low level and a low response to LH-RH. From the second week, LH increased to normal levels of follicular and luteal phases, but LH response to LH-RH in the 18-20-cycle treatment group was still significantly in a decreased state (p<0.05) even in the second week, and the recovery was delayed until after the 2nd week. LH showed a normal level for the preovulatory stage from the 3rd week after termination of treatment in the 6- and 12-cycle treatment groups, and from the 4th week in the 18-20-cycle treatment group. Additionally, the day of presumable ovulation existed in the 3rd to 4th week after termination of treatment in the former two groups and in the 4th week in the latter group. FSH in the first week after termination of treatment already showed higher levels than normal follicular and luteal phases levels in all treatment groups. Generally speaking, FSH response to LH-RH in the long treatment groups (12 and 18-20-cycles) showed remarkably higher levels than that in the 6-cycle treatment group, and in all three groups its response exceeded a normal level for the preovulatory stage.

But this increase in responsiveness could not be detected from the second cycle after termination of treatment.

Fig. 3 depicts the data in Fig. 2 from a different angle. By making the presumable ovulation date as 0 day, each week prior to this day is expressed as the -1st, -2nd, or -3rd weeks. While LH of 6- and 12-cycle treatment groups showed normal levels of follicular and luteal phases already in the -3rd week, LH of the long treatment (18-20-cycle) was a low level and a low response to LH-RH in the -3rd week. LH in the -1st week showed normal levels for the preovulatory stage in all treatment groups. Generally speaking, the LH response to LH-RH in the long treatment group (18-20-cycle) showed a lower level than the other two short treatment groups. FSH showed normal levels of follicular and luteal phases already in the -3rd week. FSH response to LH-RH gradually increased, but the longer the treatment, the more remarkable its tendency.

(b) Cases treated with tablets (mestranol 0.075 mg + lynestrenol 2.5 mg/tablet) (Figs. 4 & 5)

Fig. 4 depicts studies on the LH-RH tests conducted every week counting from the first day of the withdrawal bleeding in the first cycle after treatment. LH in both the 1st and 2nd week after termination of treatment showed significantly lower levels compared with a normal follicular and luteal phases level (p<0.05). The recovery to follicular and luteal phases levels was made in the 3rd week, and to a normal preovulatory stage level in the 4th week. In observing the difference of LH in 6- and 18-20-cycle treatment groups, both resting and response levels were higher in the former group than the latter. Additionally,
Response to LH-RH after termination of treatment with sex-steroids (mestranol 0.075 mg + lynestrenol 2.5 mg).

The day of presumable ovulation for both groups existed in the week after the 3rd week after termination of treatment. FSH showed normal levels of follicular and luteal phases already in the first week after termination of treatment, and its response to LH-RH increased weekly. However, its responsiveness rate was lower than those groups mentioned in Figs. 2 & 3.

Fig. 5 depicts the comparison in LH-RH tests of Fig. 4 in the same manner employed for Figs. 2 & 3. LH in the -3rd week showed the lowest of normal follicular and luteal phases levels, and from the -2nd week it reached these levels. In the -1st week LH showed the normal preovulatory stage level. FSH showed normal levels of follicular and luteal phases already in the -3rd week, yet in any week it increased to a level slightly higher than normal follicular and luteal
Fig. 6 compares LH-RH tests after termination of pseudopregnancy therapy and 6-cycle treatment in combination methods. LH in a pseudopregnancy therapy group showed a significantly lower level and lower response to LH-RH in both the 1st and 2nd week after termination of treatment (p<0.05), but its responsiveness was more restrained than in combination methods. The recovery of its responsiveness was delayed until after the 2nd week compared with the 2nd week in the combination methods, and the response was also a low level. Additionally, the day of presumable ovulation in the combination methods occurred in the 3rd to 4th week after termination of treatment, whereas in the pseudopregnancy

![Graph showing LH and FSH levels after termination of treatment.]

**Fig. 6** Response to LH-RH after termination of sex-steroidal treatment for 6 cycles.

Comparison between combination method & pseudopregnancy therapy.
therapy it occurred in the 4th week or later. The response in the 3rd week after termination of treatment in combination methods was higher than that in the 3rd week of the pseudopregnancy therapy. This can be attributed to the fact that in the combination methods a few cases of ovulation were already noticed in the 3rd week while no such case was detected in the pseudopregnancy therapy. FSH in the combination methods groups showed follicular and luteal phases levels already in the first week after termination of treatment, and the response increased weekly. The FSH response in the pseudopregnancy therapy group showed a lower level in the 1st week, but in the 2nd week the recovery process occurs and from the 3rd week it reaches a level equal to or higher than that of the preovulatory stage. In the pseudopregnancy therapy, moreover, FSH response to LH-RH showed a remarkable increase in the 3rd and 4th week after terminational of treatment compared with the combination methods.

(d) On various cases after long treatment with small amount of sex-steroids

(Case 1)

Fig. 7 depicts the results of serum LH and FSH levels and LH-RH tests after termination of 56-cycle treatment with tablets (mestranol 0.05 mg + norethisterone 1.0 mg/tablet). LH level compared with a normal follicular phase showed comparatively high levels (around 20 to 30 mIU/ml) from day 11 of the cycle counting from the first day of withdrawal bleeding after termination of

Fig. 7  BBT, LH, FSH & Response to LH-RH in the first cycle after termination of treatment with sex-steroids (mestranol 0.05 mg + norethisterone 1.0 mg)

length of pre-treatment menstrual cycle 35 days.
treatment, demonstrated an irregular pattern with several peaks and ovulation followed. After ovulation, LH maintained a normal level of the luteal phase. The FSH level was significantly higher than normal follicular phases after termination of treatment, and as ovulation approached it recovered a normal level of follicular phase, and ovulation followed. In the LH-RH test on day 13, LH showed a normal response of follicular and luteal phases, and FSH demonstrated increase in both resting and response levels. In the test on day 27, both LH and FSH responses to LH-RH showed normal levels of follicular phase, but FSH response did not increase. Additionally, the BBT in this period was a 65-day pattern with presumable ovulation on day 51.

(Case 2)

Fig. 8 depicts the results of LH-RH test and serum LH and FSH levels

![Graph of BBT, LH, FSH & Response to LH-RH](image)

**Fig. 8** BBT, LH, FSH & Response to LH-RH in the first cycle after termination of treatment with sex-steroids (mestranol 0.05 mg + norethisterone 1.0 mg)

length of pre-treatment menstrual cycle 28 days.
after termination of 63-cycle treatment with tablets (mestranol 0.05 mg + norethisterone 1.0 mg/tablet). LH level compared with a normal follicular phase showed higher levels (20 to 50 mIU/ml) from day 6 of the cycle counting from the first day of withdrawal bleeding after termination of treatment, and ovulation followed with a remarkable LH peak. FSH showed just about the normal level after termination of treatment. In the LH-RH test performed on day 14, LH showed normal levels of follicular and luteal phases and the resting level of FSH increased but its response was normal. In addition to these data, the BBT in this cycle demonstrated a 36-day pattern with presumable ovulation on day 23.

(e) Cases after abortion and premature delivery (Fig. 9 & 10)

Fig. 9 depicts studies on LH-RH tests conducted every week in the first cycle after abortion and premature delivery. While LH in the 10-13 weeks gestational abortion group increased to normal levels of follicular and luteal phases already in the 2nd week, LH in the 19-21 weeks abortion group showed those levels from

![Fig. 9](image-url) ![Fig. 10](image-url)

Fig. 9 (0 day: the day of abortion or premature delivery)  
Fig. 10 (0 day: the day of presumable ovulation)

Response to LH-RH after Abortion & Premature delivery.
the 3rd week and recovered to a normal level for the preovulatory stage in the
4th week. LH response to LH-RH in the 28–34 weeks premature delivery group
was still significantly in a decreased stage even in the 2nd week, and the recovery
was delayed until after the 2nd week. Its response showed a normal preovulatory
stage level from the 4th week in the premature delivery group. Additionally,
the day of presumable ovulation occurred in the 3rd week in the post gestations
in the 10–13 weeks gestational abortion group, and in the 5th week in both the
19–20 weeks abortion group and the 28–34 weeks premature delivery group.
FSH in all abortion and premature delivery groups showed higher levels than
normal follicular and luteal phases levels from the 2nd week. Though FSH
response in all three groups weekly exceeded a normal level for the preovulatory
stage, its response in the premature delivery group showed a higher level than
those in the abortion groups.

Fig. 10 depicts LH-RH tests of Fig. 9 in the same manner employed for
Figs. 2 and 3. LH of 19–21 weeks gestational abortion group and 28–34 weeks
premature delivery group showed a low level and a low response to LH-RH
prior to the -2nd week. LH response to LH-RH in the -1st week showed a normal
level for the preovulatory stage in all abortion and premature delivery groups.
However, its response in the premature delivery group showed a lower level
than those in the abortion groups. FSH response to LH-RH showed a normal
follicular and luteal phases levels already in the -4th week, and gradually in-
creased to a higher level than a normal preovulatory stage level. As ovulation
approached, the response recovered a normal preovulatory stage level, and ovula-
tion followed.

DISCUSSION

1. On menstrual cycles and BBTs before and after treatment with sex-steroids,
and before and after gestation

Regarding menstrual cycles after termination of treatment with oral con-
traceptives, Baba, et al.,9 Mizuno10 and Evrard, et al.,11 have reported that they
are prolonged in many cases. These cases of prolongation, when reviewed in
BBT analysis by this author, revealed that a lengthened low phase and a short-
ened high phase were noticeable characteristics. Murakami12 made the following
reports on 390 subjects based on their BBTs after termination of treatment:
in the first cycle, 52% showed biphasic patterns after termination of more than
two-year treatment and 85% showed biphasic patterns after termination of less
than one year treatment. In the same report, Murakami stated that the recovery
to biphasic patterns in most of the subjects was made within the 3rd cycle after
termination of treatment, yet no comparison in his report was made as to the investigation of BBTs by treatment with different types of sex-steroids.

In this author's study, 92.3% in the 12-cycle treatment group and 87.5% in the 18-20-cycle group showed a prolonged cycle in the first cycle after termination of treatment. Additionally, the longer the sex-steroidal administration, the longer delayed the day of presumable ovulation on BBT. In order to consider the possible change in the trend by subjects, this author studied a single subject with two different types of treatment, and yet obtained the same results with that from the group study (Fig. 1). However, no notable correlation was detected between the amounts administered per day (the types of sex-steroids) and the prolonged low phase in the first cycle after termination of treatment.

On the other hand, Ko recently made the following report regarding the study on re-establishment of first menstruation after gestation: the average onset date of first menstruation in puerperium was on day 67.2 in the puerpera-with-lactation group and on day 81.0 in the puerpera-without-lactation group. In the same report, it is further stated: in the puerpera, particularly whose lactation continued more than 2 months, menstrual cycles were prolonged to more than 98.5 days; in the puerpera-without-lactation group, 48.5% (32 subjects) showed a re-establishment of ovulation in the first menstrual cycle; the ovulation was observed in 14 subjects (46.7%) of the puerpera whose lactation continued less than 28 days and in 16 subjects (32.0%) of the puerpera whose lactation continued more than 29 days; above all, the earliest ovulation in the first menstrual cycle appeared on day 36 in puerperium, and the high phase was 10 days on average, and was not influenced by the length of lactation; all pregnancy in puerperium occurred only when there was just ovulation after the anovulatory menstrual cycle. These facts coincide with that of Lyon, who reported that only 5% in the first menstrual cycle in puerperium showed ovulation and the endometrium presented mostly an underdeveloped secretory pattern. However, Lyon notes, in the first ovulatory menstrual cycle after a break through bleeding without ovulation, the endometrium depicted a normal secretory pattern. Cronin made the following report for the study on the first menstrual cycle in puerperium: in the puerpera-without-lactation group, 30% showed an ovulatory cycle; the high phase in 70% of these cases continued more than 8 days. Cronin also reported in the puerpera-with-lactation group, the longer the length of lactation, the lower the ratio of ovulation re-appearance in the first menstrual cycle in puerperium.

However, no report has yet been made on the analysis of BBTs after abortion and premature delivery, nor does any report exist on the comparison of BBTs by durations of gestations.
In this author's study, the onset date of first menstruation was not delayed in the 10–13 weeks gestational abortion group. But, the date was delayed in both 19–21 weeks abortion group and 28–34 weeks premature delivery group; particularly, the delay in the 28–34 weeks group was more noticeable than in the 19–21 weeks group. The duration of high phase after the first ovulation in the post premature delivery was shorter than that in the pre-gestational period. However, the second menstrual cycle after the premature delivery recovered a normal menstrual cycle.

2. On LH-RH test and serum LH and FSH levels after treatment with sex-steroids, and after gestation

With the arrival of LH-RH test, almost direct observation of the pituitary function became possible. However, the number of reports on LH-RH test after termination of treatment with oral contraceptives are still small indeed. Nuno-kawa, et al.² have reported that response to LH-RH slightly decreased after treatment with a combination pill (ethinylestradiol 0.05 mg + ethynodiol diacetate 1.0 mg).

The results of LH-RH test after treatment with same sex-steroids for different durations are shown on Figs. 2 and 3, and these data reveal that the longer the treatment, the longer delayed the recovery of LH response to LH-RH. The sign of recovery in its response is detected from the 3rd week after termination of treatment in the case of 18–20-cycle treatment, and from the 2nd week in the case of short treatment (approximately 6-cycle); whereas FSH response to LH-RH in the first week after termination of treatment already shows normal levels of follicular and luteal phases, and gradually increases and exceeds a normal level for the prevulatory stage. This tendency is more remarkable in the longer treatment. FSH response returns to normal levels in the 2nd cycle.

The LH-RH test after treatment with the various kinds of oral contraceptives (as demonstrated in Figs. 4, 5, 7 & 8) reveals that when the amounts of sex-steroids administered were decreased (compared with Figs. 2 and 3), the recovery of LH response in the 2nd week after termination of treatment showed normal levels of follicular and luteal phases. The increase of FSH response to LH-RH was slowed by the decrease in the amounts of sex-steroids administered. In the pseudopregnancy therapy where larger amounts of sex-steroids were administered, LH response to LH-RH was strongly restrained, and its recovery process was delayed. FSH response showed a remarkable increase. Therefore, in the LH-RH test after treatment with sex-steroids, the results revealed the following: the longer the treatment and the larger the amount administered, the longer delayed the recovery of LH response to LH-RH and the more remark-
able the increase of FSH response.

Moreover, by checking 4 subjects while in the sex-steroidal treatment stage, both LH and FSH demonstrated low levels and low response to LH-RH.

Both the decrease of LH and the increase of FSH in the response to LH-RH after termination of long treatment with sex-steroids were noticed in LH-RH test after abortion and premature delivery; additionally, this result was also noticed in LH-RH test in the puerperium (Ko)\(^6\) and in the same test in the recovery process of anorexia nervosa (Kurokawa, et al.)\(^{14}\): namely, the recovery of LH response to LH-RH in the premature delivery group was delayed compared with that in the abortion groups and LH responsiveness in the former group was made to follicular and luteal phases levels in the 4th week. FSH responsiveness weekly exceeded a higher level for the preovulatory stage in the premature delivery group than that in the abortion groups. As ovulation approached, FSH recovered a normal preovulatory stage level, and ovulation followed. Then, the response of LH and FSH to LH-RH in the puerperium has recovered from the 4th week, and the FSH response at one stage exceeds the normal level but after that settles down to its normal level, establishing the first ovulation. On the other hand, in LH-RH test in recovery process of anorexia nervosa, the FSH response temporarily increases but then returns to the normal level. Thus, the increase in FSH response to LH-RH can be considered as an indication of the beginning in the recovery of pituitary, and then of ovarian function. Regarding the change in LH and FSH levels in semi-continuous measurement after termination of long treatment with sex-steroids, Flowers, et al.\(^1\) have reported that FSH level maintained a higher level than normal follicular phase after termination of treatment, and that its level showed a decrease level after ovulation, which is also demonstrated in this author’s study (Fig. 7). Flowers, et al.\(^1\) also reported that LH level demonstrated an irregular pattern with several peaks and this again is confirmed in Fig. 7. These irregular patterns with several peaks in LH and unstable FSH levels seem to show the incomplete recovery state of pituitary function at this stage, a condition that brings about the resultant poor function of corpus luteum.

In summary, it has been confirmed that a series in the recovery process in hypothalamic, pituitary and ovarian functions after termination of sex-steroidal treatment interrelated with the re-establishment of ovulation process in post abortion, post premature delivery and puerperium, through such indicators as LH-RH tests and BBT; the re-establishment of ovulation was considerably delayed after termination of treatment with large amounts of sex-steroids similarly in both post premature delivery and puerperium (Figs. 11 & 12). Initially,
therefore, the ideal estrogen and progesterone compounds for the oral contraceptive purpose should use the minimum amount of sex-steroids capable of restraining ovulation. Among the compounds being used in this research, the tablet (mestranol 0.05 mg + norethisterone 1.0 mg/tablet) satisfies the above-mentioned condition. Secondly, by different durations of continuous sex-steroidal admin-
istration, the responsiveness to LH-RH demonstrates a significantly decreased state after termination of more than 18-20-cycle treatment. The recovery process of ovulation should be checked within 18 months, which this author considers to be "one clinical control unit" in continuous administration of sex-steroids as oral contraceptives. The investigation of hypothalamic, pituitary and ovarian axis (BBT and LH-RH test), together with the estimation of usual medical examinations (liver function, blood coagulation activity and lipid metabolism, etc.), must be reviewed in determining the desirability in continuance of sex-steroidal administration, at least after termination of 18 months treatment.

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