The midluteal decline in serum estradiol levels is drastic but not deleterious for implantation after in vitro fertilization and embryo transfer in patients with normal or high responses

Shevach Friedler, M.D., Ariel Zimerman, M.D., Mori Schachter, M.D., Arieh Raziel, M.D., Deborah Strassburger, Ph.D., and Raphael Ron El, M.D.

IVF and Infertility Unit, Assaf Harofeh Medical Center, Sackler School of Medicine, Tel-Aviv University, Zerifin, Israel

Objective: To determine the impact of the peak E2 level and its midluteal decline on IVF-ET outcome in a group of normal- and high-responding patients.

Design: Retrospective analysis of IVF-ET data.

Setting: Tertiary-care, university-affiliated teaching hospital.

Patient(s): A total of 100 patients aged ≤38 years and receiving up to three embryos per transfer who underwent a similar standard controlled ovarian hyperstimulation for IVF-ET.

Intervention(s): Morning blood was collected on days 0 (hCG day), +9, and +14.

Main Outcome Measure(s): Treatment cycle hormonal characteristics and percent midluteal E2 decline in conception and nonconception cycles.

Result(s): Among all cycles, a mean decline of 95.0% in serum E2 was observed at the midluteal phase. No significant differences were found in various parameters comparing conception with nonconception cycles. Occurrence of conception did not correlate with the absolute E2 level or with percent E2 decline in good and high responders. Early spontaneous abortion occurred more frequently in high responders with >98% E2 decline; however, the difference did not reach statistical significance.

Conclusion(s): Multifactorial analysis refutes the negative role of supraphysiologic levels of E2 on the day of hCG administration or its dramatic decline at the midluteal phase on the success rate after embryo transfer. A possibly increased rate of early spontaneous abortion in the high-response group warrants further verification. (Fertil Steril 2005;83:54–60. ©2005 by American Society for Reproductive Medicine.)

Key Words: Midluteal phase, E2, implantation, IVF, pregnancy
with a daily dose of GnRH agonist (GnRH-a), who were treated in the IVF unit at Assaf Harofeh Medical Center from January 2001 to March 2002. To minimize confounding factors, the inclusion criteria to this study were as follows: patients aged ≤38 years, peak serum E2 level (on the day of hCG administration) ≥1,000 pg/mL (1,000–2,500 pg/mL defined as a good response; ≥2,500 pg/mL defined as a high response), number of retrieved mature oocytes ≥5 and number of embryos transferred ≤3, including at least one embryo of excellent morphology and cleavage rate. Only the first treatment cycle per patient was analyzed.

Controlled Ovarian Stimulation and Oocyte Retrieval

Ovarian stimulation and oocyte retrieval were performed according to a routine protocol of midluteal pituitary down-regulation, with a daily dose of GnRH-a, (nafarelin acetate nasal spray, 200 mg three times daily; or triptoreline 0.1 mg/d by SC injection) followed by COH in an individually adjusted step-up protocol with daily injection of urinary or recombinant gonadotropins. Oocytes were retrieved 36–40 hours after administration of 5,000 IU of hCG (Chorigon; Teva, Petach Tikva, Israel) by vaginal ultrasound-guided follicular puncture. The follicles were punctured once, and flushing was performed occasionally. One hundred patients, treated by conventional IVF (10 patients) or intracytoplasmic sperm injection (90 patients) met the inclusion criteria during the study period. Indications for IVF-ET included male factor (66%), tubal factor (8%), endometriosis (4%), and combination of male and female factors (10%). Fertilization was assessed on the following day, 16–18 hours after insemination or sperm injection. If two distinct pronuclei were observed, then fertilization was judged to have occurred.

Embryo Transfer, Luteal Support, and Pregnancy Evaluation

Embryonic cleavage and morphologic quality were assessed approximately 24 hours later, before ET, which was performed with a Wallace catheter. Luteal support was given to all patients, starting the day after ET (+1), until serum β-hCG measurement 14 days after ET. In this study, all patients were given micronized P (Utrogestan; Basins Iscovesco, C.T.S, Paris, France; vaginal tablets, 100 mg three times daily). Patients receiving hCG as luteal support were excluded from the study. Ethical approval was not required for this study. If a viable pregnancy was confirmed by ultrasound examination, P support was continued until 8 weeks’ gestation. Only clinical pregnancies including sonographic demonstration of a gestational sac were counted.

Hormonal Profile of the Luteal Phase

The day of hCG administration was considered day 0 of the luteal phase. Morning blood was taken on days 0 (hCG day), +9, and +14. Estradiol concentration in the serum was measured by microparticle enzyme immunoassay (MEIA), performed with an automated immunoassay analyzer (the AxSYM Estradiol system; Abbott Laboratories, Abbott Park, IL) specifically designed to accommodate MEIA (15). This method uses the microparticle coupled with each ligand (E2, P) as a competitor against the ligand in the sample. Progesterone was measured with a solid-phase chemiluminescence enzyme immunoassay (Immulite Progesterone; DPC, Los Angeles, CA). The lower limit of detection for E2 was 73 pmol/L and for progesterone was 0.6 nmol/L. The inter- and intra-assay coefficients of variation for E2 and P were 2.3% and 5.5%, and 8.0% and 4.1%, respectively.

Luteal-phase endocrine profiles were analyzed in conception and nonconception cycles to better demonstrate the hormonal milieu in the presence and absence of endogenous early levels of hCG.

The drop in serum E2 level was calculated according to the ratio of its level on the day of hCG (hCG-E2) and at the midluteal phase, 7 days after ET (ML-E2). Estradiol ratio was defined by ML-E2/hCG-E2. The percent of E2 decline was calculated as 100 − (E2 ratio × 100).

Statistical Analysis

Statistical evaluation was performed with the Student’s t-test, χ2 test, Fischer’s exact test, and analysis of variance (ANOVA), where appropriate. Differences were considered significant at P＜.05. The parameters hCG-E2, ML-E2, and percent E2 decline in conception and nonconception cycles were evaluated by receiver operating characteristics analysis (16) and calculation of the area under the curve to estimate the ability of any of these parameters to discriminate between two conditions. Multiple regression analysis was performed, correlating pregnancy occurrence and various parameters that might influence implantation, including patient age, number of mature oocytes retrieved, number of embryos transferred, hCG-E2, ML-E2, ML-P, and percent E2 decline.

RESULTS

The means (±SD) of various clinical parameters of all the patients included in the study are presented in Table 1. Their mean age was 30.0 ± 4.7 years, achieving a serum E2 level on the day of hCG administration of 3,414 ± 1,383 pg/mL (range, 1,005–7,600 pg/mL) that decreased to 157.2 ± 115.9 pg/mL (range, 14–600 pg/mL) at the midluteal phase (day +9), with a concomitant P4 level of 13.6 ± 9.8 ng/mL (range, 4.4–89.0 ng/mL). This represents a mean decline of 95.0% ± 4.7% in serum E2 at the midluteal phase. In this group of patients, the number of ova retrieved was 16 ± 6.8, fertilization rate was 50% ± 20%, and the transfer of 2 ± 0.6 embryos led to the conception of 35 clinical pregnancies, with an implantation rate of 18.1%. Sixty-five patients failed to conceive after ET, and 6 of the 35 patients who conceived (17.1%) had an early spontaneous abortion (ESA) (Table 1). None of these patients developed severe ovarian hyperstimulation syndrome necessitating hospitalization.
Various demographic and hormonal parameters were compared between conception and nonconception cycles. No significant differences were found in the various hormonal parameters examined (Student’s t-test), as presented in Table 1.

To evaluate the impact of the absolute E2 level on the day of hCG administration, the occurrence of conception was correlated with E2 level on hCG day. No significant difference was found between the mean hCG-E2 level in conception and nonconception cycles (Table 1). In addition, no correlation was found between hCG-E2 level and pregnancy rate (PR), implantation rate, or occurrence of ESA, analyzed in four different groups (ANOVA) (Table 2). Analyzing the data according to hCG-E2 of \( \leq 2,500 \) pg/mL or \( >2,500 \) pg/mL (defined as normal and high response, respectively), representing the 26th centile in our group, PR was comparable, being 34.6% (9 of 26) among normal responders and 35.1% (26 of 74) among high responders (\( P=1.0, \) Fisher’s exact test). Implantation rates were 13 of 64 (20.3%) and 31 of 179 (17.3%) and ESA rates were 1 of 9 (11.1%) and 5 of

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients</th>
<th>Conception (n = 35)</th>
<th>Nonconception (n = 65)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s age (y)</td>
<td>30.0 ± 4.7 (21–40)</td>
<td>29.4 ± 4.2 (23–40)</td>
<td>30.3 ± 4.9 (21–40)</td>
<td>NS</td>
</tr>
<tr>
<td>No. of mature oocytes retrieved</td>
<td>6.3 ± 7</td>
<td>17 ± 6</td>
<td>16.0 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>No. of ova fertilized</td>
<td>8 ± 4.9</td>
<td>9 ± 4.4</td>
<td>8 ± 5.7</td>
<td>NS</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>50 ± 20</td>
<td>53 ± 20</td>
<td>49 ± 20</td>
<td>NS</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>2.0 ± 0.6</td>
<td>2.0 ± 0.7</td>
<td>2.0 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>hCG-E2 (pg/mL)</td>
<td>3,414 ± 1,383 (1,005–7,600)</td>
<td>3,404 ± 1,378 (1,005–7,600)</td>
<td>3,420 ± 1,396 (1,170–7,499)</td>
<td>NS</td>
</tr>
<tr>
<td>Midluteal E2 (pg/mL)</td>
<td>157 ± 116 (14–600)</td>
<td>174 ± 125 (19–490)</td>
<td>148 ± 111 (14–600)</td>
<td>NS</td>
</tr>
<tr>
<td>Midluteal P (ng/mL)</td>
<td>13.6 ± 9.8 (4.4–89)</td>
<td>12.3 ± 4.7 (4.4–23)</td>
<td>14.3 ± 11.6 (5–89)</td>
<td>NS</td>
</tr>
<tr>
<td>hCG E2/ML E2</td>
<td>34.4 ± 26.5 (3.6–137.2)</td>
<td>32.9 ± 31.3 (6.1–137.2)</td>
<td>35.3 ± 23.8 (3.6–108.9)</td>
<td>NS</td>
</tr>
<tr>
<td>E2 decline (%)</td>
<td>95.0 ± 4.7 (73–99)</td>
<td>95 ± 3.4 (84–99)</td>
<td>95 ± 5.4 (73–99)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD (range). NS = not significant.

### Table 2

**Pregnancy, implantation, and ESA rates according to hCG-day E2 and mid-luteal E2 levels.**

<table>
<thead>
<tr>
<th>hCG-day E2 (pg/mL)</th>
<th>Midluteal E2 (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000–2,499</td>
<td>0–49</td>
</tr>
<tr>
<td>2,500–3,499</td>
<td>50–99</td>
</tr>
<tr>
<td>3,500–4,999</td>
<td>100–199</td>
</tr>
<tr>
<td>5,000–8,000</td>
<td>200–600</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1,000–2,499</th>
<th>2,500–3,499</th>
<th>3,500–4,999</th>
<th>5,000–8,000</th>
<th>0–49</th>
<th>50–99</th>
<th>100–199</th>
<th>200–600</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>33</td>
<td>27</td>
<td>14</td>
<td>12</td>
<td>31</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>No. of pregnancies</td>
<td>9</td>
<td>12</td>
<td>8</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>PR/ET (%)</td>
<td>34.6</td>
<td>36.4</td>
<td>29.6</td>
<td>42.8</td>
<td>25</td>
<td>35.5</td>
<td>27.6</td>
<td>46.4</td>
</tr>
<tr>
<td>No. of embryos transferred</td>
<td>64</td>
<td>83</td>
<td>67</td>
<td>29</td>
<td>30</td>
<td>81</td>
<td>69</td>
<td>63</td>
</tr>
<tr>
<td>No. of sacs</td>
<td>13</td>
<td>15</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>13</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>20.3</td>
<td>18</td>
<td>14.9</td>
<td>20.7</td>
<td>10</td>
<td>16</td>
<td>20.3</td>
<td>22.2</td>
</tr>
<tr>
<td>No. of ESA</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Data are presented as mean ± SD (range). NS = not significant.
When analyzing the data according to the four various groups were nonsignificant (ANOVA).

No significant difference was found between the mean ML-E₂ level in conception and nonconception cycles (Table 1). No correlation was found between the actual level of midluteal E₂ and the occurrence of pregnancy or implantation, as shown in Table 2, because the differences between the four various groups were nonsignificant (ANOVA). When analyzing the data according to <200 pg/mL or ≥200 pg/mL, representing the 72nd centile in our group, the differences were not statistically significant (Table 3).

Midluteal E₂ levels decreased significantly in all cycles examined (25th, 50th, and 75th centiles of the percent E₂ decline were 93.6%, 96.2%, and 97.7%, respectively [range, 73%–99%]), with no significant difference in the mean level between conception and nonconception cycles (Table 1). The distribution of percent E₂ decline among conception and nonconception cycles shows no distinction between the two groups (data not shown). When comparing the groups of <98% or ≥98% E₂ decline, representing the 80th centile, pregnancy and implantation rates were similar but the ESA rate was significantly higher in the latter group (Table 3).

Interestingly, when correlating the hCG-E₂ levels to percent E₂ decline, a significant difference was noticed in normal- vs. high-response patients. In normal responders, only 3.8% of the patients (representing a single patient) had an E₂ decline of ≥98%, compared with 25.7% in high responders (P<.01). Owing to the small size of these groups, no comparison of the outcome was done. Among the high responders (hCG-E₂ of ≥2,500 pg/mL), no significant difference was found comparing PR (34.5% vs. 36.8%) and implantation rate (18.3% vs. 15.2%) between those with <98% or ≥98% E₂ decline (χ² test). However, those with ≥98% E₂ decline had a four-fold higher ESA rate (42.8% vs. 10.5%), although the difference did not reach statistical significance (P=.34, Fisher’s exact test).

Calculating the area under the receiver operating characteristics curve assessed the predictive value of hCG-E₂, ML-E₂ or percent E₂ decline for discriminating between conception or nonconception cycles. For all three parameters examined, the areas under the curve were 0.51, 0.54, and 0.42, respectively, showing no significant differences between conception and nonconception cycles, all being close to the theoretical area of 0.5 of a test with no discriminating value. Multiple regression analysis including all patients found no significant correlation between pregnancy occurrence and various parameters, including patient age, number of mature oocytes retrieved, number of embryos transferred, hCG-E₂, ML-E₂, ML-P, and percent E₂ decline (P=.23, .75, .61, .53, .07, .23, and .08, respectively).

### DISCUSSION

The role of estrogen during the luteal phase in humans is believed to be permissive rather than obligatory (17–19). During artificial preparation of the endometrium for oocyte donation in women with no endogenous corpus luteum, pregnancies have been established without luteal estrogenic support (20–22). In addition, morphologic studies have shown no significant effect of estrogen support during the luteal phase (23, 24).

However, significant deviations from the physiologic levels of steroids produced by the ovaries might be detrimental to implantation after ET, affecting endometrial priming and receptivity, as well as oocyte maturation and quality. Two aspects of deviations from the normal levels of E₂ require attention: the markedly elevated peak levels around the day of hCG administration, and the markedly declined levels at the midluteal phase.

The negative effect of markedly elevated peak E₂ levels on implantation is a subject of debate and controversy. Whereas several investigators reported a significant negative effect, both in mice (25, 26) and in humans (1–3, 5–7, 9, 10, 12, 25, 27, 28), others found no such evidence (11, 13, 14).

Our results could not confirm an upper limit of E₂ on the day of hCG administration above which implantation rates decreased significantly, such as ≥2,320 pg/mL, reported by

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**TABLE 3**

Pregnancy, implantation, and ESA rates according to hCG-day E₂, midluteal E₂ levels, and percent E₂ decline.

<table>
<thead>
<tr>
<th></th>
<th>hCG-E₂ &lt;2,500 pg/mL</th>
<th>hCG-E₂ ≥2,500 pg/mL</th>
<th>ML-E₂ &lt;200 pg/mL</th>
<th>ML-E₂ ≥200 pg/mL</th>
<th>% E₂ decline &lt;98%</th>
<th>% E₂ decline ≥98%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>26</td>
<td>74</td>
<td>72</td>
<td>28</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>PR (%)</td>
<td>34.6a (9/26)</td>
<td>35.1a (26/74)</td>
<td>30.5a (22/72)</td>
<td>46.4a (13/28)</td>
<td>35.0a (28/80)</td>
<td>35.0a (7/20)</td>
</tr>
<tr>
<td>IR (%)</td>
<td>20.3a (13/64)</td>
<td>17.3a (31/179)</td>
<td>16.7a (30/180)</td>
<td>22.2a (14/63)</td>
<td>18.9a (37/195)</td>
<td>14.6a (7/48)</td>
</tr>
<tr>
<td>ESA (%)</td>
<td>11.1a (1/9)</td>
<td>19.2a (5/26)</td>
<td>18.2a (4/22)</td>
<td>15.4a (2/13)</td>
<td>7.1b (2/28)</td>
<td>57.1b (4/7)</td>
</tr>
</tbody>
</table>

Note: IR = implantation rate. 

aP=.05 (nonsignificant); bP=.01.

The findings of the present study concur with those of Chenette et al. (11), who reported no detrimental effect of an E2 level of >2,777 pg/mL, and those of Sharara and McClamrock (8) and Ng et al. (13), who reported no significant difference in the hCG-E2 level between cycles that did or did not result in pregnancy (2,549 pg/ml vs. 2,539 pg/ml and 2,150 pg/ml vs. 2,030 pg/ml, respectively). In a previous report by our group, similar peak E2 levels were found in conception and nonconception cycles in patients who developed severe ovarian hyperstimulation syndrome (29).

Actually, evidence in the literature indicates no toxic effect of high peak E2 levels in the fresh IVF-ET cycles on donated oocytes from high responders (5) or young healthy donors with high peak E2 (30) or compared with older ovum recipients (14) or on subsequently cryopreserved–thawed embryos (4, 12, 31). These findings reflect the exposure of the developing oocyte to a high E2 environment before oocyte retrieval and indicate that in these circumstances the implantation potential of the resulting embryos are not diminished. In view of these clinical results, it is difficult to explain the results of an in vitro study concerning murine embryos, which showed a detrimental effect of high E2 levels on embryonic development and adhesion (32). Regarding a possible detrimental effect of high peak E2 levels on the endometrium, proper evaluation is shaded by the lack of good and reliable laboratory tests for endometrial receptivity. Although variable morphologic abnormalities have been reported (33–39), others found no significant changes (40, 41). Moreover, out-of-phase biopsy might spontaneously become normal when repeated after a few days (42). These various findings stress the difficulty in the interpretation of their true meaning. One has to note that no data in the literature could be found regarding endometrial morphology in cycles in which peak E2 levels of >5,000 pg/mL were present.

Controversial results exist regarding the absolute midluteal E2 level required for implantation. Several studies have not found difference in midluteal E2 levels comparing conception with nonconception cycles, during various circumstances, including natural cycles in infertile patients (43), after COH for IVF-ET without pituitary downregulation (44–46) and COH with pituitary downregulation (8, 13). Other studies reported significantly higher midluteal E2 levels in conception cycles, during various circumstances, such as natural cycles in fertile patients (47) or after COH for IVF-ET without pituitary downregulation. After COH with pituitary downregulation for IVF, Sharara and McClamrock (8) found a lower PR in patients with a midluteal E2 level of <200 pg/mL compared with 200–600 pg/mL, but our results did not confirm these findings. Akman et al. (49) reported significantly lower hCG day +7 E2 levels in nonconception cycles compared with conception cycles in good-response patients whose excess embryos yielded blastocysts. The absence of a specific definition of an ideal luteal E2 level required for implantation does not contribute to the clarification of this issue. Furthermore, luteal support with exogenous estrogen (50, 51) or hCG (52) failed to increase PRs. Even Farhi et al. (53) found a significant increase in implantation and pregnancy rates using luteal estrogen support only in patients after a long protocol of pituitary downregulation with a depot form of GnRH-a.

Our results, showing that the midluteal E2 level did not significantly influence pregnancy and implantation rates, concur with those of Ng et al. (13). Implantations occurred over a wide range of E2 levels with this specific treatment protocol.

The notion of midluteal E2 and P4 decline after COH with pituitary downregulation for IVF when no luteal support is offered is not new (54–56); however, it was not clearly quantified. We offer to express this phenomenon by calculating the percent E2 decline. It has been suggested that this phenomenon might compromise uterine receptivity, but only a few recent studies have addressed this issue. Analyzing retrospectively the outcome of 106 IVF-ET cycles, Sharara and McClamrock (8) found that when the E2 ratio (day 0/day 8) was >5 (corresponding to 80% decline), implantation and PRs decreased significantly. These patients were treated with long or flare-up protocols for COH, and luteal support consisted of IM P (50–100 mg/d). However, Ng et al. (13) reported no adverse effect on the outcome of 763 ART cycles, despite the observed midluteal E2 decline. All patients in this study received long pituitary downregulation by a daily dose of GnRH-a, and luteal support included either 1,500 IU of hCG on the day of ET and 6 days later, or IM P (50 mg/d) or vaginal P pessaries (400 mg twice daily). The 25th, 50th, and 75th centiles of E2 ratio (day 0/day 10) were 1.8%, 2.8%, and 5.0%, respectively (meaning an E2 decline of 44.4%, 64.2%, and 80%) when hCG was used as luteal support; 3.5%, 6.3%, and 11.4% (meaning an E2 decline of 71.4%, 84.1%, and 91.2%) when P. This ratio had no significant effect on PRs.

Our findings show evidence for a significant, impressive decline in E2 levels at the midluteal phase in patients treated by a long protocol with a daily dose of GnRH-a. In contrast to the 17.9% of patients having a decline of >80% in E2 in the study by Sharara and McClamrock (8) and 25% in the study by Ng et al. (13), in our group all patients but two (98%) had an E2 decline of >80%. This decline is more pronounced in patients with higher (≥2,500 ng/mL) hCG-day E2 levels. Despite this significant decline, no detrimental influence on pregnancy or implantation rate could be detected, because E2 decline did not predict pregnancy, concurred with the report by Ng et al. (13). Patients with initially high hCG-E2 levels (≥2,500 ng/mL) and a more extreme decline in midluteal E2 levels had a higher incidence of ESA compared with patients with hCG-E2 levels of <2,500 ng/mL and percent E2 decline of <98% (42.8% vs. 11.1%, *P* = .38). Possibly the difference did not reach significance because of the small size of the groups. Interestingly, also in the report by Sharara and McClamrock (8),...
the three early miscarriages occurred in the subgroup with the highest $E_2$ decline. Nevertheless, it is tempting to suppose that because implantations did occur, the detrimental effect influenced the embryos rather than the endometrial receptivity. Because pregnancy occurrence is influenced also by several important factors, such as patient age, ovarian reserve, and number of embryos transferred, a multiple logistic regression analysis was performed, which showed that in this selected group of good and high responders, the hormonal profile of the midluteal phase, like the other parameters, had no significant impact on implantation. Because ovarian function during the luteal phase depends on the exact medications used, our findings reflect the specific protocol given in this study. Whether a milder stimulation, resulting in a lower peak $E_2$ level, will reduce the rate of ESA remains to be seen in another prospective study. In addition, because all patients received luteal support, the existence of an adverse effect on endometrial receptivity that was corrected by vaginal P administration cannot be ruled out.

We conclude that in a group of normal- and high-response patients treated with a similar long protocol of a daily dose of GnRH-a and supplemented with vaginal micronized P, neither the significant decline of midluteal $E_2$ nor the absolute serum concentration of $E_2$ correlated with implantation failure and therefore were not detrimental to IVF-ET outcome. The possible increased rate of ESA in the high-responder group warrants further verification.

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