The origin of serum progesterone during the follicular phase of menotropin-stimulated cycles*

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The study was designed to investigate the source of progesterone secretion during pituitary suppression and ovarian stimulation. It involved 416 women undergoing in-vitro fertilization (IVF) who were treated with gonadotrophin-releasing hormone agonist (GnRHa) and human menopausal gonadotrophin (HMG) (group I), 139 women undergoing ovulation induction with HMG only (group II) and nine women who were diagnosed previously as late-onset adrenal hyperplasia and treated continuously with dexamethasone, in addition to ovulation induction (group III). During HMG treatment, serum oestradiol and progesterone were measured every 1–2 days. If progesterone concentration exceeded 3.0 nmol/l, at least 36 h before human chorionic gonadotrophin (HCG) administration, the patients were prospectively randomized to treatment with dexamethasone or not and the hormones concentrations were measured again 12 h later. Mean age and pretreatment serum concentrations of dehydroepiandrosterone sulphate, androstenedione, testosterone and luteinizing hormone/follicle stimulating hormone (LH/FSH) ratio, were not significantly different in the patients with and without progesterone elevation. Pituitary down-regulation did not reduce the incidence of progesterone elevation (13.9 and 12.2% in groups I and II respectively), while in group III, progesterone concentrations did not increase. After dexamethasone administration a significant decrease in cortisol and 11-deoxycortisol but by an increase (mean SD, –5.3 ± 1.8 and 2.8 ± 4.3) in LH. After dexamethasone administration the concentrations of cortisol, 11-deoxycortisol and LH significantly decreased. Progesterone concentration was positively correlated with both oestradiol concentration (r = 0.290; P < 0.05). We conclude that at least a part of serum follicular-phase progesterone appears to be of adrenal origin. High oestrogen concentrations (or other ovarian factors) may cause changes in the hypothalamic–pituitary–adrenal axis and in adrenal enzyme activity as a part of the complex ‘cross-talk’ between the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes.

Key words: adrenal/dexamethasone/follicular phase/in-vitro fertilization/progesterone

Introduction

Serum progesterone concentrations are low (<1.5 nmol/l) during the normal early follicular phase of ovulatory cycles, but tend to increase gradually 12–24 h before the onset of the luteinizing hormone (LH) surge (Hoff et al., 1983; Yen and Jaffe, 1991; Speroff et al., 1994; Shoham et al., 1995). During controlled ovarian stimulation, a late follicular phase rise in serum progesterone has been shown to occur in 5–32% of the cycles (Schoolcraft et al., 1991; Mio et al., 1992; Silverberg et al., 1994; Fanchin et al., 1995; Harada et al., 1995; Yovel et al., 1995; Ubaldi et al., 1996a). However, the precise mechanism is unclear and the source of this progesterone has not yet been determined.

Progesterone synthesis involves the cytochrome P450 side chain cleavage enzyme, which is abundant in the corpus luteum, the theca interna of the growing follicle, the theca externa and the cortex of the adrenal gland. All of these tissues are therefore theoretically potential sources of serum follicular phase progesterone.

The aim of the present study was to determine the origin of the serum progesterone rise during controlled ovarian stimulation by comparing its incidence in ovarian stimulation cycles with and without LH suppression, comparing its changes to those in other adrenal and ovarian steroids and LH, and analysing its response to adrenocorticotropic hormone (ACTH) suppression by dexamethasone (dex) administration.

Materials and methods

Patients

The study involved 564 infertile women, aged between 21 and 44 years who had attended the Infertility Clinic and the IVF Unit in Shaare-Zedek Medical centre between January 1994 and April 1996. It included three groups. Group I comprised 416 women undergoing down-regulation/human menopausal gonadotrophin (HMG) and in-vitro fertilization (IVF)-embryo transfer. The main causes for their

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infertility were mechanical (195 patients), male factor (96 patients), polycystic ovarian syndrome (PCOS) (56 patients) and unexplained infertility (69 patients). Group II comprised 139 women undergoing induction of ovulation with HMG/human chorionic gonadotrophin (HCG) with or without intrauterine insemination. The causes for their infertility were anovulation (54 patients), male factor (35 patients) and unexplained infertility (50 patients). Group III consisted of nine women who were diagnosed as late onset adrenal hyperplasia before commencing treatment (six were treated by IVF–embryo transfer for tubal or male factor infertility and three by induction of ovulation).

Protocols

**Group I**
The patients were treated with 0.1 mg/day D-Trp⁶-LHRH (Decapeptyl; Ferring, Malmo, Sweden) s.c. from day 21 of the previous cycle until HCG administration. When 17β-estradiol concentrations were <150 pmol/l and progesterone concentrations <1.0 nmol/l (suppression of the hypothalamic–pituitary–ovarian axis), HMG (Pergonal; Teva Pharmaceutical Industries Limited, Petch Tikva, Israel) was commenced with three ampoules per day i.m. every evening for 5 days. Thereafter, the HMG dose was adjusted individually according to serum oestradiol concentrations and follicular number and size. Patients with high progesterone concentrations before commencing HMG treatment were not included in this study and have been reported elsewhere (Eldar-Geva et al., 1997). A total of 10 000 units of HCG (Chorigon; Teva Pharmaceutical Industries Limited) i.m. was administered when oestradiol concentrations were at least 3000 pmol/l, with at least three dominant follicles (>17 mm in diameter).

**Group II**
The patients received one or two ampoules of HMG per day from day 5 of the cycle for 5 days, thereafter adjusted individually according to the oestradiol concentrations and follicular number and size. HCG 10 000 units was administered when oestradiol concentrations were no more than 4400 pmol/l, with no more than three dominant follicles.

**Group III**
Dexamethasone (dex) (Rekah Pharmaceutical Products Ltd, Azor, Israel) 0.5 mg orally was administered daily in addition to all other treatment protocols.

From day 6 of HMG treatment, blood samples were collected at 0730–0830 h and serum concentration of oestradiol and progesterone were measured every other day or as needed. Serum samples were stored at −20°C until assayed for cortisol, 11-deoxycortisol (Comp-S) and LH. The patients whose serum progesterone concentration exceeded 3.0 nmol/l, at least 36 h before HCG administration, were randomly treated with dex 0.5 mg daily orally at 2000 h, or received no extra treatment. Serum progesterone concentration was measured again 12 h afterwards. The limit of 3.0 nmol/l was chosen, as this is considered by many investigators to be a value predictive of pregnancy rate in assisted reproduction (Mio et al., 1992; Silverberg et al., 1994; Fanchin et al., 1995; Harada et al., 1995). Preliminary evaluation revealed this to be the minimal dex dose required for short adrenal suppression.

Basal concentrations of dehydroepiandrosterone sulphate (DHEA-S), free testosterone, androstenedione, LH and FSH were determined retrospectively on stored blood samples obtained during the early follicular phase of a non-treatment cycle. Diagnoses of late onset adrenal hyperplasia were based on ACTH stimulation tests (New et al., 1983; Eldar-Geva et al., 1990).

**Hormone assays**
Oestradiol, progesterone, androstenedione, testosterone, cortisol and DHEA-S were measured in serum samples using solid phase radioimmunoassays (DPC Coat-A-Count, Diagnostic Products Corporation, Los Angeles, CA, USA). The intra-assay coefficients of variation (CV) were <11, 8, 6, 10, 5.1 and 4.7% respectively, and the inter-assay CVs were <11, 10, 7, 11, 6.5 and 5% respectively. The sensitivities were 10 pmol/l, 0.1, 0.1, 0.14, 8 nmol/l and 0.14 pmol/l respectively. Serum concentrations of Comp-S were measured with ImmuChem Double Antibody RIA Kit (ICN Biochemical, Inc. Costa Mesa, CA, USA). The intra-assay and inter-assay CV were <4.5 and 11.5% respectively and the sensitivity was 1 nmol/l. Serum LH and follicle stimulating hormone (FSH) concentrations were measured using the Abbott IMX system (Abbott Diagnostics, Abbott Park, IL, USA). The total CVs were <6 and 8% respectively and the sensitivity was <0.5 mIU/ml.

**Table I.** The incidence and the degree of serum progesterone (P) rise in the various patient groups

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Incidence (%)</th>
<th>Progesterone (nmol/l)</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>416</td>
<td>58 13.9 4.1 ± 2.3</td>
<td>31.7 ± 9.9</td>
</tr>
<tr>
<td>P &gt;3 nmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt;3 nmol/l</td>
<td>358</td>
<td>86.1 1.7 ± 1.9</td>
<td>32.4 ± 5.1</td>
</tr>
<tr>
<td>Group II</td>
<td>139</td>
<td>17 12.2 6.1 ± 2.4</td>
<td>30.3 ± 5.8</td>
</tr>
<tr>
<td>P &gt;3 nmol/l</td>
<td>122</td>
<td>87.8 1.6 ± 1.1</td>
<td>31.6 ± 6.5</td>
</tr>
<tr>
<td>P &lt;3 nmol/l</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>9</td>
<td>0 1.4 ± 0.1</td>
<td>30.7 ± 3.0</td>
</tr>
<tr>
<td>P &gt;3 nmol/l</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P &lt;3 nmol/l</td>
<td>9</td>
<td>100 1.4 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>

*Serum P concentrations at least 36 h before human chorionic gonadotrophin administration.

**STATISTICAL ANALYSIS**

Unless otherwise stated, all results are expressed as means ± SD. Paired and unpaired Student’s t-test, χ² analysis of variance, and Pearson’s correlation analysis were used when appropriate. *P < 0.05* was considered as being statistically significant.

**RESULTS**

The incidence of follicular phase serum progesterone elevation during ovarian stimulation cycles was not significantly different in the patient groups undergoing ovulation induction with and without pituitary down regulation (13.9 and 12.2% for group I and group II respectively, *P = 0.6; χ² test* (Table I). By contrast, none of the nine women treated continuously with dex (group III) had elevated serum progesterone concentrations. There was no difference in mean age between the various groups.

To examine the hypothesis that the adrenal gland is the source of progesterone secretion during ovarian stimulation, we determined whether the increased serum progesterone concentration could be reversed by suppression of ACTH by dex, in comparison to no additional treatment (Table II and Figure 1a). In 30 out of 33 women (91%) in groups I and II, serum progesterone concentrations decreased 12 h following dex administration, compared to seven out of 42 (16.6%) at the same time in the untreated groups (*P < 0.0005; χ² test*). Mean serum progesterone concentration after dex was significantly lower than before treatment (*P < 0.005; paired Student’s t-test).
are indicated by the horizontal lines.

We compared the changes in serum progesterone concentrations to those of other adrenal and ovarian steroids in the dexamethasone (dex) administration. In all dex-treated patients, cortisol concentrations decreased considerably 12 h after dex administration. Comp-S concentrations also decreased considerably in the blood samples, in which it could be measured but which could not be tested for statistical significance.

To search for late-onset adrenal hyperplasia we performed an ACTH stimulation test on 10 patients with elevated progesterone and 12 without, all from group I. All patients, except one with elevated progesterone, had a normal response to ACTH stimulation. This single patient demonstrated partial 11-hydroxylase deficiency, and although the main indication for IVF was male factor infertility, she also had polycystic ovarian syndrome (PCOS). Pretreatment mean serum DHEA-S concentration was not statistically significantly different between the groups with and without elevated progesterone values (Table III).

Pretreatment early follicular serum androstenedione, free testosterone and LH/FSH ratio were not significantly different between the group with elevated progesterone concentrations and the group without (Table III). Likewise, the distribution of the main indication for IVF treatment was similar in both groups. Oestradiol concentrations and the number of oocytes retrieved were significantly higher in the group with elevated progesterone. A significant correlation was found between progesterone and oestradiol concentrations on the day of HCG administration (r = 0.290, P < 0.05) and the number of oocytes retrieved (r = 0.207, P < 0.05).

The increase in serum progesterone concentration during late follicular phase was accompanied by an increase in serum LH concentration in 84% of the patients in group I and in all patients in group II. However, no significant difference in LH concentration was found between those patients who demonstrated an increase in progesterone concentrations and those who did not. The change in LH concentrations was significantly lower in group II. However, no significant difference in LH concentration was found between the group with elevated progesterone, had a normal response to ACTH stimulation test on 10 patients with elevated progesterone, and the group without (Table III).

Pretreatment early follicular serum androstenedione, free testosterone and LH/FSH ratio were not significantly different between the group with elevated progesterone concentrations and the group without (Table III). Likewise, the distribution of the main indication for IVF treatment was similar in both groups. Oestradiol concentrations and the number of oocytes retrieved were significantly higher in the group with elevated progesterone. A significant correlation was found between progesterone and oestradiol concentrations on the day of HCG administration (r = 0.290, P < 0.05) and the number of oocytes retrieved (r = 0.207, P < 0.05).

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We compared the changes in serum progesterone concentrations to those of other adrenal and ovarian steroids in the dex-treated group I patients (Figure 1a–d). Serum concentrations of cortisol and Comp-S did not increase during HMG treatment; indeed, most women exhibited a subtle decrease in these parameters (Figure 1b, c). In all patients cortisol concentrations decreased considerably 12 h after dex administration (P < 0.0005, paired Student’s t-test. Comp-S concentrations also decreased considerably in the blood samples, in which it could be measured but which could not be tested for statistical significance).

To search for late-onset adrenal hyperplasia we performed an ACTH stimulation test on 10 patients with elevated progesterone and 12 without, all from group I. All patients, except one with elevated progesterone, had a normal response to ACTH stimulation. This single patient demonstrated partial 11-hydroxylase deficiency, and although the main indication for IVF was male factor infertility, she also had polycystic ovarian syndrome (PCOS). Pretreatment mean serum DHEA-S concentration was not statistically significantly different between the groups with and without elevated progesterone values (Table III).

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Table II. Changes in serum progesterone (P) concentrations 12 h after Dexamethasone (dex) administration

<table>
<thead>
<tr>
<th>Group</th>
<th>ΔP (nmol/l)a</th>
<th>Incidence of decreased P (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dex +</td>
<td>-2.1 ± 1.4</td>
<td>-4.4 to +1.3 b</td>
</tr>
<tr>
<td>dex -</td>
<td>+1.9 ± 1.9</td>
<td>-0.4 to +5.0</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dex +</td>
<td>-1.6 ± 1.2</td>
<td>-4.8 to +0.3 b</td>
</tr>
<tr>
<td>dex -</td>
<td>+4.2 ± 4.8</td>
<td>+1.3 to +10.5</td>
</tr>
</tbody>
</table>

aDifference between serum P concentrations before and after dexamethasone administration. Ranges in brackets.

bP < 0.005 versus dex −, unpaired Student’s t-test.

Table III. Serum hormone concentrations and the main indication for IVF in group I patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P &gt;3 nmol/l</th>
<th>P &lt;3 nmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA-S (µmol/l)a</td>
<td>5.34 ± 3.18</td>
<td>4.96 ± 3.70</td>
</tr>
<tr>
<td>Free testosterone (pmol/l)a</td>
<td>6.85 ± 6.50</td>
<td>6.30 ± 2.30</td>
</tr>
<tr>
<td>LH/FSH ratiob</td>
<td>1.05 ± 1.00</td>
<td>0.97 ± 0.32</td>
</tr>
<tr>
<td>Androstenedione (nmol/l)c</td>
<td>6.24 ± 3.73</td>
<td>6.18 ± 2.50</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>7578 ± 2650d</td>
<td>4418 ± 4824</td>
</tr>
<tr>
<td>Egg number</td>
<td>15.50 ± 6.70d</td>
<td>7.81 ± 3.73</td>
</tr>
</tbody>
</table>

Main indication for IVF (%):

- Mechanical: 36.2 (21) 48.6 (174)
- Male factor: 32.8 % (19) 21.5 (77)
- PCOS: 17.2 (10) 12.8 (46)
- Unexplained: 13.9 (8) 17.0 (61)

a Serum samples taken during the early follicular phase of an untreated cycle.

b On the day of HCG administration.

cP < 0.05 versus P <3 nmol/l, unpaired Student’s t-test.

dPatient numbers are in brackets.

DHEA-S = dihydroepiandrosterone sulphate; P = progesterone, LH = luteinizing hormone, FSH = follicle stimulating hormone, PCOS = polycystic ovarian syndrome (PCOS). Pretreatment mean serum DHEA-S concentration was not statistically significantly different between the groups with and without elevated progesterone values (Table III).

Pretreatment early follicular serum androstenedione, free testosterone and LH/FSH ratio were not significantly different between the group with elevated progesterone concentrations and the group without (Table III). Likewise, the distribution of the main indication for IVF treatment was similar in both groups. Oestradiol concentrations and the number of oocytes retrieved were significantly higher in the group with elevated progesterone. A significant correlation was found between progesterone and oestradiol concentrations on the day of HCG administration (r = 0.290, P < 0.05) and the number of oocytes retrieved (r = 0.207, P < 0.05).
Student’s t-test) (Figure 1d). In the non-treated group, at the same time, the mean LH concentration did not change significantly (range from increase by 0.4 mIU/ml to decrease by 1.6 mIU/ml). In all three groups, none of the women whose serum progesterone concentrations remained <3 nmol/l during the follicular phase demonstrated an elevation of >0.5 mIU/ml in serum LH concentrations.

Discussion

The origin of late follicular phase progesterone has been assumed by many investigators to be due to direct stimulation by the gonadotrophins, mainly LH, on the ovary (Yen and Jaffe, 1991; Speroff et al., 1994; Ubaldi et al., 1996a). On the basis of this assumption, we would have expected to see a much lower incidence of elevated serum progesterone in the group of patients who were under pituitary-suppression (group I), than in the group who were not (group II). In our study, however, an increase in serum progesterone concentrations occurred with a similar frequency in both patient groups (Table I). Our results agree with those of Yovel et al. (1995), who found no difference in the frequency of elevated progesterone concentration before HCG administration in IVF patients treated with or without gonadotrophin-releasing hormone agonists (GnRHa) and similar doses of HMG. This implies that early elevation in LH secretion is not the exclusive cause of elevated progesterone.

Our results indicate that at least a part of serum late follicular progesterone is of adrenal origin. Our results are in accordance with those of Judd et al. (1992), who found that the pulsatility of progesterone during the follicular phase was not related to LH pulsatility or to manipulations of LH pulsatility, and that dex brought about a reduction in serum progesterone concentrations during the natural follicular phase. They concluded that the dominant source of progesterone in the follicular phase is the adrenal gland under the control of ACTH. Peterson (1971) found that the adrenal vein progesterone concentration exceeded that in peripheral blood. Fanchin et al. (1995) observed that during ovarian stimulation with HMG for IVF–embryo transfer, peak concentrations of plasma progesterone, testosterone and androstenedione concentrations occurred during the early morning, coincidental with the circadian elevation in ACTH and adrenal function. Casson et al. (1996) showed that adrenal DHEA-S secretion was augmented by ovarian hyperstimulation. Their study, in accordance with ours, implies that ovari an hyperstimulation may induce adrenal steroid synthesis. In rats, oestrogen administration causes an elevation in ACTH which induces adrenal progesterone secretion by impairment of the glucocorticoid receptor-mediated negative feedback on CRF and ACTH secretion (Burgess and Handa, 1992). This subtle increase in serum progesterone stimulates secretion of LH. Whether similar or alternate interactions between the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes exist in human is as yet unknown. Our results, and those discussed above, imply that the increase in oestradiol concentration in stimulated cycles may increase ACTH concentrations, which would stimulate progesterone secretion from the adrenals.

We found, in common with others, a positive correlation between serum progesterone concentrations during the late follicular phase of ovarian stimulation cycles with both serum oestradiol concentrations (Schoolcraft et al., 1991; Mio et al., 1992; Silverberg et al., 1994; Levy et al., 1995; Ubaldi et al., 1995) and the number of oocytes retrieved (Mio et al., 1992; Silverberg et al., 1994; Bustillo et al., 1995; Levy et al., 1995). These data are consistent with the hypothesis that serum progesterone concentration reflects the pooled secretion from multiple mature ovarian follicles. Some authors have suggested that the increased exposure to oestradiol and FSH induces LH receptivity in granulosa cells (Schoolcraft et al., 1991; Hillier, 1996; Ubaldi et al., 1996a), which stimulates ovarian progesterone secretion. However, as discussed above, higher oestradiol concentrations could increase ACTH secretion, which stimulates adrenal progesterone secretion.

In our study, we attempted to measure cortisol and Comp-S concentrations, as both are synthesized exclusively in the adrenal gland and thus are sensitive markers of adrenal function. We did not attempt to measure either 17-OH-progesterone, as this is secreted by both ovaries and adrenals, or DHEA-S, as this would not be expected to change during the short period of adrenal suppression (dex) applied in our study. We found that the rise in adrenal progesterone secretion was not accompanied by a rise in other adrenal steroids, namely cortisol and Comp-S. Casson et al. (1996) also found that the rise in basal and ACTH-stimulated serum DHEA-S concentrations during ovarian hyperstimulation had no effect on serum cortisol concentrations. In a previous study, we found a secondary defect in 11β-hydroxylase activity in women with 21-hydroxylase deficient late-onset congenital adrenal hyperplasia (Eldar-Geva et al., 1990). This enzyme is involved in the synthesis of Comp-S and cortisol. In-vitro studies have shown the inhibition of 11β-hydroxylase by ovarian steroids (Sharma et al., 1963). Ditkoff et al. (1995) have explored the role of oestrogen in inducing enhanced adrenal sensitivity in patients with PCOS. They found that patients with PCO had increased responses of 11β-hydroxyandrostenedione and DHEA and an increase in the maximal ratios of androstenedione/ACTH and DHEA/ACTH after corticotrophin-releasing hormone (CRH) treatment. After pituitary down-regulation with GnRHa treatment, these ratios were significantly suppressed, but returned to baseline after oestradiol was added. The baseline and stimulated cortisol concentrations were not affected by oestradiol concentrations. These studies, in accordance with ours, imply that oestrogen can increase ACTH-stimulated adrenal androgen synthesis with no accompanying increase in cortisol concentrations.

Recently, Fanchin et al. (1997) investigated the effect of continuous dex administration on progesterone and androgen profiles during ovarian stimulation for IVF–embryo transfer. After pituitary suppression, administration of dex followed by HMG was performed. Dex produced a greater reduction in progesterone and androgen concentrations than that achieved by GnRHa alone. In agreement with our results, they found that in patients treated with dex serum progesterone concentrations on the day of HCG administration were significantly lower. However, the absolute increment in serum progesterone
and androgens was unaltered by dexamethasone. They concluded that the rise in serum progesterone concentrations during ovarian stimulation resulted solely from an effect of exogenous gonadotrophins on the ovary. However, continuous suppression of the hypothalamic–pituitary–adrenal axis could obscure subtle changes occurring during ovarian stimulation with this axis intact.

We have also demonstrated that the elevation of progesterone concentrations was accompanied by an increase in LH concentrations (Figure 1d), in spite of pituitary suppression by GnRHa. This increment was significantly smaller than in the group with intact pituitary–ovarian axis. The increase in LH could not be explained by escape from pituitary down regulation, since all women received GnRHa (Decapeptyl) daily. The very short half-life of LH (Yen and Jaffe, 1991) negates the contribution of HMG itself to the measured serum LH. Our results are in agreement with those of Ubaldi et al. (1995), who found that the mean LH concentrations were significantly higher in GnRHa/HMG cycles with progesterone. This increment was significantly smaller than in the group with high doses of GnRHa (Broekmans et al., 1996) or use of a GnRH antagonist (Ubaldi et al., 1996a), complete suppression of LH could not be achieved.

The pituitary response to GnRH is influenced by ovarian steroids, including oestrogen and progesterone, and by less well-characterized ovarian peptide hormones (Yen and Jaffe, 1991; Speroff et al., 1994, Bergendahl et al., 1996). Araki et al. (1985) have shown that in women, oestrogens can reduce pituitary desensitization produced by continuous GnRH administration, resulting in prolonged release of LH. Although they used different methods from those used in our IVF patients, this mechanism may explain the increase in LH secretion despite continuous GnRH administration. The increased secretion of oestradiol or some peptide hormones by the developing ovarian follicles during ovarian stimulation may change the level of pituitary desensitization and cause an increase in LH secretion. During the natural cycle, the small increase in progesterone concentration during very late follicular phase has been demonstrated to facilitate the LH surge or even to be essential for it to occur (Yen and Jaffe, 1991). This implies that, despite pituitary suppression, the small increase in serum progesterone of adrenal origin may cause a subtle increase in LH concentrations which induces secretion of progesterone of ovarian origin.

However, there are other interpretations. Adrenal steroids or ACTH may influence ovarian function. Jacobs et al. (1991) have shown that immunoreactive ACTH is present in the human ovary and in particular the oocyte and the interstitium, although they proposed that ovarian ACTH may act in a paracrine rather than an endocrine fashion. Michael et al. (1993) reported that cortisol and dexamethasone directly inhibit LH-stimulated pregonenolone production. Pituitary ACTH may act directly on the ovary, or dexamethasone may directly affect GnRH or LH secretion. We do not know of a sensitive ovarian steroid marker which would enable us to distinguish clearly between the two possible sources of progesterone during ovarian stimulation.

In summary, we have demonstrated that the late follicular phase of GnRHa/HMG ovarian stimulation cycles was accompanied by an increase in serum progesterone and LH, both reversible by the administration of dexamethasone. We conclude that at least a part of follicular phase progesterone appears to be of adrenal origin. High oestrogen concentrations (or other ovarian factors) may cause certain changes in the hypothalamic–pituitary–adrenal axis and in adrenal enzyme activity as a part of the complex ‘cross-talk’ between the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes.

Acknowledgement

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References


Harada, T., Yoshida, S., Katagiri, C et al. (1995) Reduced implantation rate of the ovary, or dexamethasone may directly affect GnRH or LH secretion. We do not know of a sensitive ovarian steroid marker which would enable us to distinguish clearly between the two possible sources of progesterone during ovarian stimulation.

In summary, we have demonstrated that the late follicular phase of GnRHa/HMG ovarian stimulation cycles was accompanied by an increase in serum progesterone and LH, both reversible by the administration of dexamethasone. We conclude that at least a part of follicular phase progesterone appears to be of adrenal origin. High oestrogen concentrations (or other ovarian factors) may cause certain changes in the hypothalamic–pituitary–adrenal axis and in adrenal enzyme activity as a part of the complex ‘cross-talk’ between the hypothalamic–pituitary–ovarian and the hypothalamic–pituitary–adrenal axes.

References


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