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GnRH antagonists in the treatment of gynecological and breast cancers

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Abstract

Approximately 80% of human ovarian and endometrial cancers and 50% of breast cancers express GnRH and its receptor as part of an autocrine regulatory system. After binding of its ligand the tumor GnRH receptor couples to G-protein \( \alpha_i \) and activates a variety of intracellular signaling mechanisms. (1) Through activation of a protein tyrosine phosphatase, autophosphorylation of growth factor receptors is reverted leading to an inhibition of mitogenic signaling and reduced cell proliferation. (2) Through activation of nuclear factor kappa B antiapoptotic mechanisms are induced protecting tumor cells from apoptosis induced, for example, by doxorubicin. (3) Through activation of the Jun kinase pathway AP-1 is induced, leading to cell cycle arrest in the G0/G1 phase. It seems reasonable to speculate that this system enables the tumor cell to reduce proliferation and to activate repair mechanisms while being protected simultaneously from apoptosis. Interestingly, GnRH antagonists show the same activity in this system as agonists, indicating that the dichotomy GnRH agonist–GnRH antagonist defined in the pituitary gonadotrope is not valid for the tumor GnRH system. Recently, a second type of GnRH receptor, specific for GnRH-II, has been identified in ovarian and endometrial cancers, which transmits significantly stronger antiproliferative effects than the GnRH-I receptor. GnRH antagonists have agonistic effects on this type II receptor. In animal models of human cancers, GnRH antagonists had stronger antitumor effects than GnRH agonists. Therefore, we performed a phase II clinical trial with the GnRH antagonist, cetrorelix (10 mg/day), in patients with ovarian or mullerian carcinoma refractory to platinum chemotherapy. Of 17 evaluable patients treated with cetrorelix, 3 obtained a partial remission (18%) which lasted for 2 to 6 months. Furthermore, 6 patients experienced disease stabilization (35%) for up to 1 year. In this very refractory patient population (median number of prior chemotherapies = 3) these results are quite remarkable when compared with palliative chemotherapy. In addition, cytotoxic GnRH analogs have been developed, where for example doxorubicin was covalently coupled to GnRH analogs. These compounds have superior antitumor effects in cancers expressing GnRH receptors as compared with native doxorubicin and allow for a targeted cytotoxic chemotherapy of gynecologic and breast cancers.

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Introduction

The hypothalamic decapeptide gonadotropin hormone releasing hormone (GnRH), also called luteinizing hormone-releasing hormone (LHRH), functions as a key hormone in the regulation of mammalian reproduction (Schally 1994, Stojilkovic & Catt 1995, Stanislaus et al. 1998). In addition to its classic hypophysiotropic action, GnRH might function as a modulator of the activity of diverse systems in the brain and many peripheral organs (reviewed in Gründker et al. 2002a). It has been suggested that an autocrine/paracrine function of GnRH exists for example in the placenta, granulosa cells, myometrium, and lymphoid cells (reviewed in Emons et al. 1997, Gründker et al. 2002a).
**GnRH systems in human cancers**

Since 1985 the expression of GnRH and its receptor as well as direct antiproliferative effects of GnRH and its analogs have been demonstrated in a number of malignant human tumors, including cancers of the breast (Blankenstein et al. 1985, Miller et al. 1985, Eidne et al. 1987, Fekete et al. 1989, Baumann et al. 1993), ovary (Emons et al. 1989, Palwa et al. 1989, Emons et al. 1993a, Ohno et al. 1993, Thompson et al. 1991, Yano et al. 1994a,b, Kakar et al. 1994, Irmel et al. 1995), and endometrium (Srkalovic et al. 1990, Palwa et al. 1991, Emons et al. 1993b, Imai et al. 1994a,b, Irmel et al. 1994, Chatzaki et al. 1996). About 50% of breast, 70% of ovarian and 80% of endometrial cancers express GnRH and its receptor (Emons et al. 1997, Gründker et al. 2002a, Völker et al. 2002) (Table 1). These findings suggested the presence of an autocrine regulatory system in these cancers based on GnRH. Studies performed in our laboratory have demonstrated that the proliferation of ovarian cancer cells was significantly increased after treatment with an antiserum to GnRH, suggesting that GnRH produced by the tumor cells acts as a negative autocrine regulator of proliferation (Emons et al. 2000a). Native GnRH and GnRH agonists were found to inhibit in a dose- and time-dependent manner the proliferation of human breast, ovarian and endometrial cancer cell lines (reviewed in Emons et al. 1997, Gründker et al. 2002a). In most cancer cell lines tested, GnRH antagonists also induced a time- and dose-dependent inhibition of proliferation indicating that the dichotomy of GnRH agonist–GnRH antagonist as defined in pituitary gonadotropes does not apply to the GnRH system in human cancers. Here, antagonists act like agonists (Emons et al. 1997, Gründker et al. 2002a) (Fig. 1). Some investigators failed to detect direct antitumor effects of GnRH analogs in human cancer cell lines or observed them only at high concentrations of GnRH analog or short-term incubation (24 or 48 h) were used (Emons et al. 2000a, Völker et al. 2002). Thus our data and most reports in the literature suggest that in the majority of ovarian and endometrial cancers, GnRH and its receptor are part of a negative autocrine system which might be used therapeutically to inhibit cell proliferation by the application of GnRH analogs.

**Signal transduction of the GnRH system in human breast, ovarian and endometrial cancers**

During the last decade, the signal transduction mechanism mediating the antiproliferative effects of GnRH analogs in

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**Table 1** Expression of GnRH-I, GnRH-I receptors and biological effects of GnRH-I analogs. Data were obtained in primary cancers and/or respective tumor cell lines. Numbers in brackets indicate the available data on percentages of primary cancers expressing GnRH-I, GnRH-I receptor or respective mRNAs.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Expression of GnRH-I</th>
<th>Expression of GnRH-I receptor</th>
<th>Inhibitory effects of GnRH-I analogs on</th>
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<tr>
<td></td>
<td>Immuno/ bioactivity</td>
<td>mRNA</td>
<td>Radioreceptor-assay mRNA</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(&gt;50%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>(&gt;80%)</td>
<td>(&gt;80%)</td>
<td>(&gt;80%)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>(&gt;80%)</td>
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GnRH receptor which might explain this phenomenon. Also, could not find mutations or splice variants in the tumor system and the tumor GnRH systems remains unclear, as we and breast cancers (Emons et al. 1996a). The reason for these differences between the pituitary and the tumor GnRH systems induces three different mechanisms are activated by the GnRH receptor in tumor cells. (1) Stimulation of a protein tyrosine phosphatase, counter-acting autophosphorylation of growth factor receptors, leading to an inhibition of mitogenic signaling and reduced cell proliferation. (2) Stimulation of nuclear factor κB, leading to a protection of tumor cells from apoptosis. (3) Induction of AP-1 through activation of the Jun kinase pathway leading to cell cycle arrest in the G1 phase. It seems

Figure 1 Effects of 6 days of treatment with increasing concentrations of the GnRH agonist triptorelin (left panel) or the GnRH antagonist cetrorelix (right panel) on the proliferation of the endometrial cancer cell line Ishikawa. Cell number is expressed as a percentage of the controls (C, vehicle only = 100%). Each column represents the mean ± S.E. of data obtained from three (triptorelin) or four (cetrorelix) independent experiments run in quadruplicate in three or four different passages of the cell line. Analysis of variance: P<0.001. Newman Keuls: a, P<0.01 vs. c; b, P<0.01 vs. 10⁻¹¹ mol/l; c, P<0.01 vs. 10⁻⁹ mol/l; d, P<0.01 vs. 10⁻⁷ mol/l. Experiments using endometrial cancer cell line Hec-1A and ovarian cancer cell line EFO-21 gave comparable results. From Emons et al. 1993b, with permission. © 1993, The Endocrine Society.

gynecological and breast cancers has been elucidated. After binding of its ligand, the GnRH receptor in cancers couples to G protein αi and activates a phosphotyrosine phosphatase (Lee et al. 1991, Furui et al. 1995, Imai et al. 1996a,b, Emons et al. 1996a, Gründker et al. 2001a). This phosphotyrosine phosphatase dephosphorylates epidermal growth factor (EGF) receptors (Gründker et al. 2001a). As a result, mitogenic signaling induced by binding of EGF to its receptor is abrogated leading to a suppression of EGF-induced activation of mitogen-activated protein kinase (MAPK) (Emons et al. 1996a), c-fos expression (Fig. 2) (Gründker et al. 2000a), and EGF-induced proliferation (Emons et al. 1996a) (Fig. 3). This signaling mechanism of GnRH receptors in human cancers is quite different from that in pituitary gonadotropes, where GnRH receptors couple to G protein αq and activate phospholipase C and protein kinase C (reviewed in Gründker et al. 2002a). Although G protein αq is expressed in the cancer cells (Gründker et al. 2001a), and phospholipase C and protein kinase C can be activated by pharmacological stimuli (Emons et al. 1996a), these compounds of the pituitary GnRH system are not involved in the mediation of antimitogenic effects of GnRH in gynecological and breast cancers (Emons et al. 1996a, Gründker et al. 2001a). The reason for these differences between the pituitary and the tumor GnRH systems remains unclear, as we could not find mutations or splice variants in the tumor GnRH receptor which might explain this phenomenon. Also, the finding that GnRH antagonists act like agonists in human cancers cannot be explained by mutations or splice variants of the GnRH receptor (Gründker et al. 2001a) and awaits further clarification.

Recently, it became evident that it is not only mitogenic signaling of growth factor receptors that is modulated by GnRH in human cancers. We could show that, in addition, nuclear factor κB is activated by GnRH in human ovarian and endometrial cancer cells (Gründker et al. 2000b). This effect is also mediated through G protein αi and leads to an inhibition of tumor cell apoptosis induced by for example the cytotoxic agent doxorubicin (Gründker et al. 2000b) (Fig. 3). Finally, we could show that binding of GnRH analogs to their receptors in cancers induces c-jun mRNA expression, c-Jun phosphorylation and AP-1 activation, again mediated through G protein αi (Gründker et al. 2001b). GnRH agonists induce Jun D-DNA binding in cancer cells, reduce DNA synthesis and lead to accumulation of cells in the G1 phase of the cell cycle (Günther et al. 2002) (Fig. 3). Thus, at least three different mechanisms are activated by the GnRH receptor in tumor cells. (1) Stimulation of a protein tyrosine phosphatase, counter-acting autophosphorylation of growth factor receptors, leading to an inhibition of mitogenic signaling and reduced cell proliferation. (2) Stimulation of nuclear factor κB, leading to a protection of tumor cells from apoptosis. (3) Induction of AP-1 through activation of the Jun kinase pathway leading to cell cycle arrest in the G1 phase. It seems
reasonable to speculate that this GnRH system enables the tumor cell to reduce proliferation and activate repair mechanisms while being protected simultaneously from apoptosis.

**Clinical applications of GnRH agonists in breast, ovarian and endometrial cancers**

GnRH agonists have become a cornerstone in the systemic treatment of premenopausal women with estrogen-dependent breast cancer, both in the adjuvant as well as in the metastatic situation (Jonat 2001). Here, the essential mode of action of GnRH agonists is down-regulation of pituitary gonadotropin secretion, leading to a suppression of ovarian estrogen production, a state called reversible medical castration (Emons & Schally 1994). It remains unclear whether direct effects of GnRH analogs on breast cancer cells contribute to their marked efficacy mediated through estrogen withdrawal (reviewed in Emons & Schally 1994). In ovarian cancer, several phase II clinical trials have been performed in patients with relapsed, mostly platinum-resistant disease. Of 245 published patients, 23 (9%) had an objective remission and 64 (26%) had disease stabilization (Emons & Schulz 2000). In a large study by the European Organisation for Research and Treatment of Cancer (EORTC), only eleven (16%) out of 68 evaluable patients with progressive ovarian cancer treated with a GnRH agonist had disease stabilization, while no objective responses were observed. Median survival for patients with stable disease was 17 months, whereas for all patients it was 4 months (Duffaud et al. 2001).

It might be argued that the efficacy of an endocrine therapy like GnRH agonists might be reduced in patients with relapsed ovarian cancer refractory to standard chemotherapy. In an attempt to use GnRH agonist as a first-line systemic therapy, a prospective double-blind randomized trial was performed in which 135 patients with stage III or IV epithelial ovarian carcinoma received either monthly injections of the GnRH agonist [n-Trp6]GnRH (Triptorelin, 3.75 mg) or placebo until their deaths or termination of the trial respectively. All patients had standard cytoreductive surgery and were treated with a standard platinum-based chemotherapy, and, if necessary, with second- or third-line cytotoxic regimens. Progression-free and overall survival in patients receiving the GnRH agonist were not significantly different from that of patients receiving placebo (Emons et al. 1996b). At the time this study was designed and performed, the direct anti-apoptotic effects of GnRH agonists in tumor cells were not yet known (Gründker et al. 2000b). In view of our present knowledge, the lack of activity of the GnRH agonist in combination with chemotherapy might be interpreted as a neutralization of its direct antiproliferative effects by its anti-apoptotic activity, protecting tumor cells, at least in part, from apoptosis induced by chemotherapy.

Also, in patients with relapsed or metastatic endometrial cancer GnRH agonists have been used. Up to now, the treatment of 144 women suffering from disseminated endometrial cancer with GnRH agonists has been reported. Objective remissions have been seen in 12% and stable diseases have been observed in 31% of these women (reviewed in Emons et al. 2000b, Noci et al. 2001).

Thus, single agent therapy with GnRH agonists in doses used for suppression of pituitary gonadotropin secretion has a modest activity in patients with relapsed or disseminated ovarian or endometrial cancer leading, in some cases, to long-lasting remissions or disease stabilization. As this treatment is virtually devoid of side effects, it remains a valid option in patients who will not tolerate or accept further chemotherapy. A combination of GnRH agonists with chemotherapy is probably not efficacious as the direct anti-proliferative effects of GnRH agonists are neutralized by their anti-apoptotic activity.

**Clinical applications of GnRH antagonists**

Using the human ovarian cancer cell line OV-1063 xenografted into nude mice, Yano et al. (1994b) demonstrated a significant inhibition of tumor growth by chronic treatment with the GnRH antagonist Cetrorelix but not with the GnRH antagonist Cetrorelix-induced inhibition of EGF-induced c-fos expression. C-fos expression of quiescent MCF-7 breast cancer cells (A = control = quiescent cells) and after treatment with 100 nM EGF (10 min) without (B) or with (C) previous treatment (15 min) with the GnRH antagonist Cetrorelix (CETRO; 100 nM) or with previous treatment with the GnRH antagonist Cetrorelix and with (2 ng/ml) PTX (D). After treatment with EGF, a significant increase in c-fos expression was observed (P < 0.001) (B). After treatment with Cetrorelix followed by EGF, no increase in c-fos expression was observed (C). After treatment with PTX, Cetrorelix-induced inhibition of EGF-induced c-fos expression was blocked indicating mediation through G-protein α (P < 0.001) (D). Columns represent means ± S.E.M. of data obtained from four independent experiments run in duplicate in four different passages of each cell line. a, P < 0.001 vs. control (A); b, P > 0.001 vs. EGF (B); c, P < 0.001 vs. EGF/CETRO (C).
agonist Triptorelin. As both GnRH analogs induced a comparable suppression of the pituitary–gonadal axis, the authors speculated that antitumor effects of cetrorelix were exerted directly on GnRH receptors in tumors (Yano et al. 1994a,b). Assuming that the direct antitumor effects of GnRH antagonists might be superior to those of GnRH agonists, we designed a clinical trial with the GnRH antagonist cetrorelix in patients with ovarian or Mullerian carcinoma refractory to platinum chemotherapy. In former trials with GnRH agonists, doses of the analogs (3–8 mg/month) had been used that were sufficient to suppress pituitary gonadotropin secretion. Tissue concentrations of LHRH agonists obtained with these conventional depot preparations of GnRH agonists (nM range, Emons & Schally 1994) might have been only marginally active at the tumor cell level. Therefore, in this trial, a cetrorelix dose of 10 mg/day was chosen in an effort to increase analog concentration at the tumor cells to a more efficacious level. In addition, during the first week of the trial, a pharmacological study was performed injecting increasing doses (1 mg/day to 10 mg/day) before the maintenance dose of 10 mg/day of cetrorelix was administered to all patients throughout the study. In this trial, performed at the MD Anderson Cancer Center, Houston, Texas, USA and at the University of Marburg, Germany, seventeen evaluable patients were treated. All patients had relapsed after at least one standard chemotherapy, 4 had two preceding chemotherapies, 5 had three prior chemotherapies and 8 had more than three chemotherapies before entering into the trial. Five patients had prior immuno- and three a prior hormonal therapy. Even in this group of heavily pretreated patients with refractory ovarian cancer, three patients (18%) experienced a partial remission with cetrorelix treatment lasting 2, 6 and 7 months, while 6 women (35%) had disease stabilization for 1–12 months. Median survival was 17 months. Toxicities included 1 anaphylactoid reaction (grade 4) controlled by corticoids and cimetidine, grade 2 histamine reaction (2 patients), grade 2 arthralgia (1 patient), minor hot flushes, headache, and local skin reaction at the injection site. With more experience on possible side effects, anaphylactoid and histamine reactions could be safely prevented by oral diphenhydramine (25 mg) and, if needed, cimetidine (300 mg/day) orally. With an injected dose of 10 mg/day, cetrorelix plasma concentrations remained constant and ranged between 30 and 60 ng/ml (20–40 nM). At this concentration significant antitumor effects of cetrorelix had been observed in vitro (Emons & Schally 1994). Thus, cetrorelix has some activity against ovarian cancer and, with appropriate co-medication, is well tolerated. In this very refractory patient population these
results are quite remarkable when compared with palliative chemotherapy, which induced similar duration of remission and overall survival (Ozols 1997).

Future perspectives

Cytotoxic GnRH analogs

To further increase the efficacy of GnRH receptor-mediated antitumor therapy, cytotoxic GnRH analogs have been developed, where a cytotoxic agent is covalently linked to a GnRH analog (Schally & Nagy 1999). These GnRH analogs that are covalently coupled to cytotoxic radicals bind specifically to GnRH receptors with their peptide moiety and act as chemotherapeutic agents after internalization of the ligand–receptor complex or at the membrane of cancer cells (Schally & Nagy 1999). Thus, these cytotoxic GnRH analogs should selectively affect those cells that express GnRH receptors and would exert fewer side effects than unconjugated cytotoxic agents (Schally & Nagy 1999). We could demonstrate that such a cytotoxic GnRH analog, AN-152, in which doxorubicin is linked to agonist carrier [D-Lys₆]GnRH is selectively accumulated in the nucleus of human ovarian or endometrial cancer cell lines that express GnRH receptors. This uptake of AN-152 could be competitively inhibited by an excess of a GnRH agonist. In cancer cell lines that do not express GnRH receptors, no intracellular accumulation of AN-152 could be detected (Westphalen et al. 2000). In 3 out of 4 GnRH receptor-positive cell lines, AN-152 was more effective than doxorubicin in inhibiting cell proliferation in vitro. These results suggest a selective receptor-mediated action of AN-152 in GnRH receptor-positive cell lines and encouraged us to study the efficacy of AN-152 in vivo. GnRH receptor-positive HECA-1B endometrial cancers and NIH: OVCAR-3 ovarian cancers, and GnRH receptor-negative SK-OV3 ovarian cancers were xenografted into nude mice. Animals bearing these tumors subcutaneously were injected intravenously with saline solution (control), AN-152 or doxorubicin at equimolar doses. The tumor volumes of GnRH receptor-positive HECA-1B and NIH: OVCAR-3 cancers were reduced significantly 1 week after treatment with AN-152 at 700 nmol/20 g or at 300 nmol/20 g. No toxic side effects were observed. Treatment with doxorubicin arrested tumor growth but did not reduce tumor volume. Doxorubicin at 700 nmol/20 g caused a high mortality rate and at 300 nmol/20 g caused a loss of body weight but no deaths occurred. The growth of GnRH receptor-negative SK-OV-3 cancers was not affected by AN-152. Thus, the cytotoxic GnRH analog, AN-152, is more effective and less toxic than the cytotoxic radical doxorubicin on GnRH receptor-positive tumors (Gründker et al. 2002b) (Fig. 4). In addition, we found that normal human non-reproductive tissues, hematopoietic stem cells, and vaginal tissue did not express GnRH receptors (Gründker et al. 2002b). It was only in the human ovary, endometrium, myometrium, fallopian tube and the cervix, i.e. tissues derived from the mullerian epithelium, that expression of GnRH receptors was detected (Gründker et al. 2002b). The ovaries, fallopian tubes and the uterus are removed during curative surgery of ovarian or endometrial cancer. Even if they are not removed due to advanced stage of disease, it would not be harmful if they were affected by AN-152 therapy. Therefore AN-152 appears to be a suitable drug for a more efficacious and less toxic targeted chemotherapy for endometrial and ovarian cancers (Gründker et al. 2002b). Clinical trials with AN-152 are in preparation. GnRH analogs bearing a more potent cytotoxic radical like 2-pyrrolino doxorubicin might be even more efficacious than AN-152 (Schally & Nagy 1999, Gründker et al. 2002b).

GnRH-II and its receptor

In non-mammalian vertebrates, it became evident that three structural variants of GnRH were present in individual species. A similar situation seems to exist in mammals. One of these GnRH variants is GnRH-II (also called chicken GnRH-II) which is entirely conserved in structure from fish to mammals (White et al. 1998, Urbanski et al. 1999). Recently, Millar et al. cloned a type II GnRH receptor from the marmoset monkey which is highly selective for GnRH-II (Millar et al. 2001). At the same time Neill et al. cloned the GnRH-II receptor from the rhesus monkey (Neill et al. 2001). Using RT-PCR and Southern blot analysis we could demonstrate the expression of GnRH-II receptor mRNA in human endometrial and ovarian cancer cell lines (Gründker et al. 2002c). The proliferation of these cell lines was reduced in a dose- and time-dependent manner by native GnRH-II (Fig. 5). These effects were significantly more potent than the antiproliferative effects of equimolar doses of the GnRH-I agonist triptorelin. In the GnRH-II receptor-positive but GnRH-I receptor-negative ovarian cancer cell line SK-OV-3 native GnRH-II but not the GnRH-I agonist triptorelin had antiproliferative effects (Gründker et al. 2002c). These findings open a new field of research on the role of GnRH-II in human cancers. As the anti-proliferative activity of native GnRH-II is significantly superior to that of the GnRH-I superagonists, superactive analogs of GnRH-II might become efficacious drugs for the therapy of human cancers expressing GnRH-II receptors.

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Figure 4 (A and B) Tumor volume of NIH: OVCAR-3 human ovarian cancers (A; GnRH-I receptor-positive) and SK-OV-3 human ovarian cancers (B; GnRH-I receptor-negative) xenografted into nude mice. Saline (control), doxorubicin (300 nmol/20 g) and AN-152 (300 nmol/20 g) were administered intravenously once on day 0. The numbers in brackets represent the numbers of animals alive. All experimental groups consisted of 5 animals. (C) Body weight of nude mice bearing HEC-1B human endometrial tumors. Saline (control), doxorubicin (300 nmol/20 g) and AN-152 (300 nmol/20 g) were administered intravenously once on day 0. All experimental groups consisted of 5 animals. Experiments in nude mice bearing NIH: OVCAR-3 or SK-OV-3 human ovarian cancers gave comparable results. Results are means with vertical bars representing S.E.M. *P<0.05 versus control, **P<0.01 versus control, ***P<0.05 versus day 0 for AN-152; ns, not significant. From Gründker et al. 2002, with permission. © 2002, American Journal of Obstetrics and Gynecology.

Figure 5 Time-course experiments on cell proliferation of human endometrial cancer cell lines Hec-1A (A) and Ishikawa (B) and human ovarian cancer cell lines EFO-21 (C) and SK-OV-3 (D). Cells were incubated without (control) or with 10 µM native GnRH-II or with 10 µM GnRH-I agonist triptorelin. Cell number is given as a percentage of controls (100%). Each point represents the mean ± S.E.M. of three independent experiments, performed using different passages of the respective cell line in quadruple determinations. a, P<0.001 versus control; b, P<0.05 versus control; c, P<0.05 versus triptorelin treatment; d, P<0.001 versus triptorelin treatment. From Gründker et al. 2002c, with permission. © 2002, The Endocrine Society.

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