The role of selective oestrogen receptor modulators in the treatment of endometrial bleeding in women using long-acting progestin contraception

D.R. Grow¹ and M.T. Reece

Department of Obstetrics and Gynecology, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA 01199, USA

¹To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Baystate Medical Center, Tufts University School of Medicine, Springfield, MA 01199, USA
E-mail: daniel.grow@bhs.org

This paper explores the concept that endometrial breakthrough bleeding results from the stimulatory effects of oestrogen in the endometrium. Though ‘progestin-only’ contraceptive regimens have long been associated with user dissatisfaction because of unpredictable vaginal bleeding, it is likely that the substantial contribution of endogenous ovarian oestradiol during such treatments predisposes the bleeding problems. Oestrogen causes endometrial proliferation, hyperplasia and neoplasia if unopposed. Oestrogen allows production of growth factors supporting angiogenesis which results in an abundance of dilated or fragile endothelial surface blood vessels, predisposing this tissue to bleeding when these vessels lose competence. Key words: endometrial bleeding/mifepristone/progestin-only contraception/selective oestrogen receptor modulators

Introduction

Antagonism or withdrawal of oestrogenic stimulation from the endometrium causes atrophy and usually amenorrhoea. Data from some non-human primate studies using gonadotrophin-releasing hormone anologue (GnRHa), mifepristone and onapristone are presented herein and show that virtually complete amenorrhoea is produced in the non-human primate with oestrogen action suppressed. An emerging class of drugs with competitive anti-oestrogen properties in the uterus has become clinically available and may prove useful.

Selective oestrogen receptor modulators (SERM) may play an important role in contraception; opposing the perhaps unneeded oestrogenic stimulation of the endometrium, but allowing oestrogen action at other sites. Though experience with tamoxifen has proven imperfect because of some uterotrophic effects, raloxifene or other newer compounds may show promise. Combination of SERM and progestin for contraception may allow complete amenorrhoea.

Progestin is itself a non-competitive anti-oestrogen in the endometrium. If progestin contraception is combined with a competitive oestrogen antagonist such as raloxifene, endometrial breakthrough bleeding may be prevented.

Several recent studies have demonstrated that the endometrium of progestin-only contraceptive users contains an abnormally high concentration of capillaries and thin-walled venules. Through identification of vascular endothelial cells with anti-CD34 antibody, the endometrial microvascular density of 54 normally cycling control volunteers was compared to the endometrial microvascular density of 42 women exposed to Norplant® for 3–12 months. The microvascular density of Norplant users was increased nearly 60% over the normal controls (P < 0.001) (Rogers et al., 1993). This change was found by several other investigators who found that the concentration of endothelial cells per mm² is higher after Norplant (Goodger...
et al., 1994) and that pathologically enlarged venous sinusoids are ubiquitous in endometrial specimens obtained after Norplant treatment (Runic et al., 1997). Norplant endometrium was always noted to be thinner than control endometrium, with a varied histology that usually included a basalis-type appearance, signs of haemorrhage, and some dilated and congested subendothelial vessels (Rogers, 1996). Endometrial bleeding during chronic progestin-only contraception differs from cyclical menstrual bleeding in that during normal menstruation bleeding emanates from endometrial spiral arterioles, whereas breakthrough bleeding probably originates from thin-walled capillaries or dilated veins and is limited to patchy areas of the endometrial surface (Hickey et al., 1996).

**Oestrogen supplementation**

Several studies have investigated the effectiveness of oestrogen supplementation of progestin-only contraceptive users in an attempt to decrease the frequency of breakthrough bleeding. These efforts have brought little success. A study by the World Health Organization (WHO) treated bleeding users of depomedroxyprogesterone acetate (DMPA) with ethinyl oestradiol, oestrone sulphate, or placebo for a fortnight. Ethinyl oestradiol users had less bleeding, but experienced a more unpredictable pattern than the other two groups. In the long-term, there were no differences between the bleeding patterns or the discontinuation rates for any reason in the three groups. The most important reason for discontinuation for each group remained 'menstrual problems' (Said et al., 1996). Similar studies in Norplant users have yielded similar results. The first (Diaz et al., 1990) showed a marginal benefit when irregular bleeders were treated with ethinyl oestradiol as compared to those Norplant bleeders treated with ibuprofen or placebo. This finding has not been reproducible. A recent comparison of Norplant users treated with transdermal oestradiol or placebo showed no decrease in breakthrough bleeding in the oestradiol group (Boonkasemsanti et al., 1996). Another study of Norplant users compared bleeding rates after the addition of ethinyl oestradiol, ethinyl oestradiol and progestin, or placebo. The ethinyl oestradiol group was not improved over placebo, but the group with added progestin did have reduced bleeding (Alvarez-Sanchez et al., 1996). This finding of increasing progestin causing decreased breakthrough bleeding is consistent with the original pharmacological trials using DMPA performed by the WHO in which a 150 mg dose was compared to a 100 mg dose, both given every 3 months. The group receiving 150 mg had lower levels of circulating oestradiol and a higher incidence of amenorrhoea (Said et al., 1987). Both of these studies are consistent with the hypothesis that decreasing oestrogen activity (decreasing oestradiol concentration or decreasing oestrogen receptor via excess progestin) decreases endometrial breakthrough bleeding.

Oestrogen-deficient states, i.e. childhood, menopause, castration and gonadotropin releasing hormone (GnRH) agonist therapy, produce a thin and atrophic endometrium and almost uniformly result in absolute freedom from vaginal bleeding. Conditions of oestrogen excess [i.e. polycystic ovary syndrome, oestrogen (only) replacement therapy, and chronic anovulation] result in exuberant endometrial proliferation and frequent bouts of endometrial bleeding. Oestrogen-rich conditions during which cyclical exposure to progestin occurs (i.e. the natural ovarian cycle, cyclical oral contraceptive pills) result in regular endometrial bleeding, predictably occurring after the progestin exposure is discontinued. Oestrogen-rich conditions during which chronic exposure to progestin occurs (i.e. continuous oral contraceptive pills, progestin-only pills, and progestin implants or injections) result in high rates of unpredictable endometrial bleeding.

Steroid control of the endometrial vasculature can operate through various direct and indirect mechanisms, with up to 30 genes relevant to vascular function having consensus oestrogen response elements in their promoter regions (Rogers, 1996). Decreasing oestrogen action through either hypo-oestrogenism or oestrogen antagonism could thus effect a whole cascade of growth factors which have a role in angiogenesis.

**Use of anti-angiogenic compounds**

Recent pharmacological advances have produced compounds effective in preventing the proliferation of new blood vessels in oestrogen responsive
Table I. Summary of menstrual calendars, frequency of ovulation, and circulating serum oestradiol for three groups of eight monkeys each followed daily for 1 year

<table>
<thead>
<tr>
<th>Group</th>
<th>Menstrual days (total)</th>
<th>Menstrual days/month</th>
<th>Ovulations (total)</th>
<th>Ovulations per year</th>
<th>Oestradiol (pmol/ml ± SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone</td>
<td>5</td>
<td>0.05</td>
<td>6</td>
<td>0.75</td>
<td>231 ± 12</td>
</tr>
<tr>
<td>GnRHa</td>
<td>45</td>
<td>0.47</td>
<td>6</td>
<td>0.75</td>
<td>77.1 ± 2.5b</td>
</tr>
<tr>
<td>Control</td>
<td>422a</td>
<td>4.4</td>
<td>100a</td>
<td>12.5</td>
<td>231 ± 13</td>
</tr>
</tbody>
</table>

The mifepristone group received weekly i.m. injections of 2 mg/kg. The gonadotrophin releasing hormone agonist (GnRHa) group received monthly depot injections of leuprolide acetate. The control group received weekly saline injections. During 2920 days of follow up for each group (8 years), there were only 5 days of menses noted in the mifepristone group versus 422 days in the control group. Serum oestradiol (sampled weekly) was virtually identical in the mifepristone and control groups and suppressed during GnRHa.

aP < 0.001 compared to all other treatment groups.
bP < 0.05 compared to all other treatment groups.

Oestrogen antagonists

Some recent experiments in non-human primates show the utility of mifepristone, a non-competitive oestrogen antagonist in preventing vaginal bleeding. Mifepristone caused virtually absolute amenorrhoea. Grow et al. studied a population of intact, regularly cycling monkeys which had been placed on chronic GnRH-agonist therapy, mifepristone, or saline, to study the effects on ovulation and menstrual frequency. There were eight monkeys per group and each underwent 12 months of treatment. As shown in Table I, neither the GnRH-agonist nor the mifepristone-treated monkeys ovulated. The GnRH-agonist treated monkeys became severely hypo-oestrogenic and had only 0.47 bleeding days/month on average compared to 4.4 bleeding days/month for the regularly menstruating saline group. Interestingly, the mifepristone group maintained mid-follicular serum oestradiol concentrations but showed extremely rare menstrual bleeding, only 0.05 menstrual days/month. In 8 monkey-years of follow-up (2920 monkey-days of daily menstrual examinations), there were only five days in which any vaginal bleeding was noted. This equates to less than one bleeding day per monkey per year. The anti-oestrogen effect of mifepristone effectively antagonized the circulating endogenous oestradiol and prevented endometrial proliferation and vascularization. It prevented venous ectasia. Both the mifepristone group and the GnRHa group showed thin and atrophic endometrium (Grow et al., 1996, 1998).

Basic fibroblast growth factor (bFGF) is a potent peptide regulator of new blood vessel growth (angiogenesis) in many tissues (Gospodarowicz et al., 1987). It is chemotactic and mitogenic for endothelial cells in vitro, inducing endothelial cell production of factors involved in the breakdown of the basement membrane and the migration of capillary endothelial cells into collagen matrices to form capillary-type tubes. Ovarian steroids modulate the synthesis and function of bFGF in endometrial cells (Presta, 1988), suggesting that these growth factors may play a role in endometrial growth and vascularization. Recombinant bFGF stimulates plasminogen activator production in endometrium (Presta, 1988) and proliferation of human endometrial stromal cells (Irwin et al., 1991). Likewise, VEGF is critically involved with the construction and remodelling of new blood vessels throughout the body via binding to its transmembrane tyrosine kinase receptor, VEGF-R1 (Smith, 1995; Hanahan, 1997). Several species
Selective oestrogen receptor modulators

Table II. Immunohistochemical scores were calculated as intensity (0 to 3 scale) multiplied by proportion of cells staining positive

<table>
<thead>
<tr>
<th></th>
<th>VEGF</th>
<th>Flt-1</th>
<th>bFGF Glands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glands</td>
<td>Stroma</td>
<td>Glands</td>
</tr>
<tr>
<td>Proliferative phase</td>
<td>246 ± 25</td>
<td>224 ± 13</td>
<td>108 ± 21</td>
</tr>
<tr>
<td>Secretory phase</td>
<td>253 ± 22</td>
<td>204 ± 22</td>
<td>166 ± 23</td>
</tr>
<tr>
<td>All cycling</td>
<td>250 ± 15</td>
<td>213 ± 15</td>
<td>139 ± 18</td>
</tr>
<tr>
<td>GnRHa</td>
<td>183 ± 71</td>
<td>233 ± 17</td>
<td>12 ± 6a</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>168 ± 16</td>
<td>208 ± 8</td>
<td>49 ± 10a</td>
</tr>
</tbody>
</table>

Intact cycling monkeys were biopsied at random times during the cycle. All monkeys were in treatment at least three months before a biopsy was obtained. Values are mean ± SEM.

VEGF = vascular endothelial growth factor; bFGF = basic fibroblast growth factor; GnRHa = gonadotrophin releasing hormone agonist.

of VEGF are expressed in the endometrium with both VEGF-1 and VEGF-2 known to have biological effect (Charnock-Jones, 1993).

Immunohistochemical quantification of the concentration of the angiogenesis growth factors bFGF, VEGF and VEGF-R1 were performed on endometrial samples collected from the monkeys discussed above (Grow et al., 1998). Each monkey was on treatment for at least 3 months before biopsies were performed. The cycling control primate endometrium showed a significantly higher mean bFGF intensity score as well as for VEGF-R1 when compared to treatment groups (see Table II). These findings suggest that the oestrogen antagonism properties of mifepristone and the hypo-oestrogenism induced by GnRHa were effective from the perspective of preventing endometrial bFGF and VEGF-R1 expression. Inhibition of this or other oestrogen-responsive mitogens seems to allow endometrial vascular stability and prevent endometrial bleeding. Evaluation of the monkey endometrium for vascular endothelial histology remains difficult, as the antigens on the endometrial vascular cells react differently than human tissues to factor VIII and CD34 antibodies.

Endometrial vascular stabilization has also been demonstrated in an oestrogen-rich environment with the non-competitive oestrogen antagonist onapristone. Williams et al. (1997) treated a group of castrate (surgically menopausal) monkeys with combination oestrogen/progestin replacement therapy. One subgroup was given a monthly dose of onapristone, while the other subgroup received monthly placebo. Daily vaginal swab was performed to determine the incidence of menstrual bleeding. The onapristone group experienced a 10-fold reduction in the incidence of breakthrough bleeding.

Recently, a third antiprogestin and non-competitive anti-oestrogenic compound (ORG31710) was used to reduce the incidence of breakthrough bleeding in non-human primates receiving progestin-only contraception. Monkeys given daily desogestrel were given monthly ORG31710 or placebo. ORG31710 treatment profoundly reduced the incidence of breakthrough bleeding associated with the daily use of oral progestin (Williams et al., 1997).

Tamoxifen

Tamoxifen is an anti-oestrogen and anti-angiogenic agent that enjoys widespread clinical use for its ability to prevent the spread of breast cancer in humans. Tamoxifen is a triphenylethylene derivative that is a competitive antagonist of oestrogen, but seems to have anti-angiogenic effects independent of, and in addition to, its anti-oestrogen effects. In a study by Lindner et al. (1997), nude mice were implanted with MCF-7 breast carcinoma (oestrogen dependent) or NIH-OVCAR-3 ovarian carcinoma (oestrogen independent). These mice were then treated with tamoxifen or placebo with attention to tumour size and the concentration of blood vessels in the periphery at study end. Tamoxifen treatment decreased the number of vessels by 68% in the MCF-7 tumours, and by
73% in the NIH-OVCAR-3 tumours. In addition, tamoxifen treatment resulted in inhibition of growth for the MCF-7 tumours and NIH-OVCAR-7 tumours by 67% and 88% respectively (Lindner, 1997).

Tamoxifen and other anti-oestrogens inhibit angiogenesis in the chick egg chorio-allantoic membrane (Gagliardi, 1993). This inhibition of angiogenesis was even observed in the presence of 5-fold increased concentrations of 17β-oestradiol. This again suggests anti-angiogenic action that is independent of the oestrogen receptor.

The effects of tamoxifen have been demonstrated in the uteri of rats where treatment causes a decrease in uterine weight, epithelial thickness and in the number of glands (Patriarca et al., 1996). Tamoxifen is a competitive anti-oestrogen, but its precise action sometimes depends on the presence of oestrogen. In the absence of oestradiol, tamoxifen promotes some endometrial growth, but in the presence of oestradiol, growth is inhibited. Proliferation of the endometrium has been reported in 15–40% of postmenopausal breast cancer patients (Lahti et al., 1993; Kedar et al., 1994). Endometrial polyps also develop in postmenopausal tamoxifen-treated women (Lahti et al., 1993). The tamoxifen–oestrogen receptor complex may bind to DNA but has a different effect on the transcription-activating function than that induced by oestrogen. It may be agonistic or antagonistic based upon its effect on gene transcription within a given cell type, thus it is often referred to as a selective oestrogen receptor modulator.

Tamoxifen has been used extensively in clinical trials and in postmenopausal breast cancer patients for many years. In postmenopausal (hypo-oestrogenic) women it has an oestrogenic action in bone and on serum lipids, but only a very weak oestrogenic effect in the uterus (Powles et al., 1996). The endometrium remains relatively thin, mean thickness 5–8 mm, and patients uncommonly suffer from vaginal bleeding (Hann et al., 1997). Uterine blood flow is a phenomenon controlled by oestrogen and can be measured in the uterine artery by Doppler technology. Postmenopausal breast cancer patients receiving tamoxifen have greater uterine blood flow than observed with no hormonal therapy, but less than observed with typical dosages of oestrogen used for replacement therapy (Achiron et al., 1995).

There are a limited number of studies reporting premenopausal women using tamoxifen. Tamoxifen causes a slight elevation in pituitary gonadotrophins, and enhances oestradiol production in the ovary. Premenopausal women on tamoxifen alone experience regular menstrual cycles, but serum oestradiol levels are generally double the levels observed without tamoxifen (Shushan et al., 1996). Tamoxifen has been used, like clomiphene citrate, for ovulation induction or ovarian stimulation in the treatment of infertility. Premenopausal women treated with tamoxifen sometimes develop ovarian cysts. These cysts are rarely larger than 4 cm and resolve soon after discontinuation of the tamoxifen (Shushan et al., 1996). When it is preferable to continue tamoxifen even in the face of a cystic ovary (premenopausal breast cancer), the ovarian cysts will also resolve after treatment with a GnRH-agonist (suppression of pituitary gonadotrophins) (Shulman et al., 1995).

Tamoxifen has rarely been combined with progestin, but a few reports exist. One showed profound suppression of both oestrogen and progesterone receptors in the endometrium, which was atrophic and decidualized (Cohen et al., 1997). Few data are available on the levels of pituitary gonadotrophin observed with combination progestin and tamoxifen. As progestin alone causes suppression of pituitary LH and FSH secretion, and tamoxifen alone causes mild elevation, little measurable change would be anticipated with the combination.

**Raloxifene**

Raloxifene is a benzothiophene derivative with structural similarities to the triphenylethylene anti-oestrogens such as tamoxifen and clomiphene citrate. These compounds each inhibit oestradiol-induced activation of oestrogen response element-containing genes to various extents. Recent works have suggested that oestradiol metabolites and raloxifene are able to activate the transforming growth factor β3 gene via a polypurine sequence dubbed the raloxifene response element, which does not require binding to the oestrogen receptor (Yang et al., 1996). Multiple oestrogenic DNA response elements help explain the tissue-selective
Selective oestrogen receptor modulators

agonistic/antagonistic properties of these compounds. Additionally, oestrogen receptor subtype (ER) alpha and beta may be selectively or preferentially expressed in different tissues. As each receptor subtype shows unique binding characteristics and different transcriptional products, different oestrogenic compounds will produce different oestrogenic responses in different tissues (Labrie et al., 1999). Researchers continue to seek the perfect designer oestrogen, whereby the beneficial effects of oestrogen on brain, bone and blood vessels are preserved while the risk of endometrial hyperplasia is minimized. The role of raloxifene in preventing breast cancer is currently being investigated.

Raloxifene is a selective oestrogen receptor modulator (like tamoxifen) that also has anti-oestrogen and anti-angiogenic effects but appears to be more oestrogen antagonistic in the endometrium, but with agonistic effects in other tissues (Sato et al., 1996). When given to ovariectomized rats, raloxifene produced almost undetectable changes in the endometrium, yet was quite effective in the prevention of bone loss. Tamoxifen showed similar effects, but there was more endometrial response and less bone preservation in the same study. The anti-angiogenic properties of raloxifene have not been evaluated to date.

Postmenopausal women \( (n = 601) \) receiving raloxifene or placebo for 24 months had no measurable increase in endometrial thickness by ultrasound, with the raloxifene group preserving their total body bone mineral density and decreasing their total cholesterol and low density lipoprotein. In the postmenopausal women, raloxifene was well tolerated with no significant increase in any adverse event, nor difference in the proportion of raloxifene-treated subjects leaving the study because of an adverse event (Delmas et al., 1997). Raloxifene-treated subjects had no increased risk of endometrial bleeding over placebo treated. Another short-term (eight week) study showed no oestrogenic effects on the endometrium of postmenopausal subjects (Boss et al., 1997). Raloxifene is now approved by the US Food and Drug Administration for use by postmenopausal women in the prevention of osteoporosis. It is administered daily.

A single recent study focuses on the effects of raloxifene in premenopausal subjects (Baker et al., 1998). Raloxifene does not inhibit ovulation nor affect the general pattern of oestradiol, progesterone, FSH or LH production. However, raloxifene did increase the area under the curve for the entire cycle for both oestradiol and FSH. This is similar to the effects seen with tamoxifen. There was a non-significant trend toward a decrease in maximal endometrial thickness in the raloxifene group compared to controls. Endometrial biopsies showed a significant decrease in the number of gland mitoses in the raloxifene cycle with an increase in the number of cells displaying cell death. The vaginal cytology during raloxifene showed a lower maturation index. Sex hormone binding globulin concentrations were higher during the cycle of raloxifene treatment compared to pretreatment with all measured values remaining in the normal range (a hepatic oestrogen agonistic effect). Raloxifene was well tolerated at all (100 mg and 200 mg) doses with no adverse effects noted. A single subject reported possible hot flashes.

Raloxifene has never been administered with an exogenous progestin. Expectations are that it would act much like tamoxifen on the hypothalamic–pituitary–ovarian system. Endometrium should remain thin and decidualized with atrophy likely in some subjects despite early follicular levels of circulating ovarian oestradiol. We anticipate that endometrial vascularity will be less than with exogenous progestin alone.

Progestin and SERM contraception

Depomedroxyprogesterone acetate, Norplant, and other forms of ‘progestin-only’ contraception enjoy high marks for ease of use but suffer from low continuation rates because of high rates of breakthrough bleeding (Belsey et al., 1986; Westfall et al., 1996). Though only inhibiting ovulation with moderate success, the contraceptive efficacy of the injectable agents is very high. Progestins act on the hypothalamic–pituitary–ovarian endometrial axis in at least two places. Firstly, it decreases pituitary production of gonadotrophins, mostly LH, so that the LH surge occurs unreliably and ovulation is sometimes prevented. Because modest pituitary FSH production still occurs, ovarian oestradiol production continues at midfollicular range serum levels (Mishell, 1996). Oestradiol is thus present
D.R.Grow and M.T.Reece

for endometrial effects. Secondly, progestin has a potent effect in the uterus, causing endometrial atrophy and decidualization. Progestins, agonists and antagonists, have an anti-oestrogen effect without binding to the oestrogen receptor. This non-competitive inhibition of oestrogen receptor transcriptional activity is possible when the A form of progesterone receptor is present. When the human progesterone receptor (hPR-A) form is occupied by a progestin agonist or antagonist, a dose-dependent inhibition of oestrogen receptor transcriptional activity occurs (McDonnell, 1994). Thus, it is likely that hPR-A, when bound, sequesters a transcriptional factor or co-factor required for human oestrogen receptor (hER) transcriptional activity (McDonnell, 1994). Progestational agents thus act as non-competitive anti-oestrogens in organs like the human uterus which contains both A and B forms of progesterone receptor.

The oestrogen antagonism in the endometrium by progestins used in progestin-only contraception perhaps is incomplete. In some women, there is still enough transcription of angiogenesis growth factors to allow the development of dilated ectatic venules under the endometrial surface. Is oestrogen stimulation an absolute requirement for the growth factor production? If these growth factors are transcribed in conjunction with oestrogen response elements, would competitive inhibition of endogenous oestradiol (by SERM) in the endometrium suppress microvascular proliferation in this tissue?

There seems to be sufficient evidence to support a study to test the hypothesis that combination progestin/anti-oestrogen (SERM) contraception will allow better user satisfaction as a result of decreased endometrial breakthrough bleeding. Scientific data regarding SERM compounds in the human endometrium is lacking. Likewise, specific knowledge about the role of angiogenesis growth factors in the human endometrium is sketchy. These new anti-oestrogen compounds provide tools to gather information about ways to resolve endometrial angiogenesis. Can endometrial vascular competence be improved by antagonizing oestradiol?

Complexities of this drug combination may present. For example, will pituitary suppression of LH secretion be altered by addition of a SERM? Will pituitary FSH production rise (as with clomiphene citrate) allowing more ovarian oestradiol production? Will the competitive inhibition of oestradiol by SERM be able adequately to antagonize oestradiol in the endometrium? It will be fascinating to learn the answers to some of these questions.

Conclusions

Endometrial breakthrough bleeding is very problematic, particularly for those reproductive age women on progestin-only contraceptive regimens. It is likely that endogenous ovarian oestrogen allows development of excessive endometrial microvasculature, with fragile and dilated ectatic venules under the endometrial surface. We present evidence from monkey studies utilizing mifepristone that antagonism of oestrogen decreases angiogenic growth factors, and promotes a stable endometrium. Much work remains in the human. The new class of compounds called selective oestrogen receptor modulators (SERMs) may be uniquely qualified to antagonize the action of oestrogen at the endometrium, yet allow beneficial oestrogenic effects at other organs.

Though the SERM compounds antagonize the actions of oestradiol differently than mifepristone, the combination use of SERM and progestin for contraception will probably cause increased endometrial atrophy and perhaps provide a new therapeutic regimen for the treatment of, or prevention of, breakthrough vaginal bleeding.

References


Gagliardi, A. and Collins, D.C. (1993) Inhibition of
Boonkasemsanti, W., Reinprayoon, D., Pruksananoda,
preliminary results from a hysteroscopic study. *Hum.
steroids and growth factors differentially regulate the
growth and differentiation of cultured human
dometrial stromal cells. *Endocrinology*, 129,
Kedar, R.P., Bourne, T.H., Powles, T.J. et al. (1994)
effects of tamoxifen uterus and ovaries of
postmenopausal women in a randomized breast cancer
(SCH 567668), a third generation SERM acting as a
pure antiestrogen in the mammary gland and
dometrium. *J. Steroid Biochem. Mol. Biol.*, 69,
Lahti, E., Blanco, G., Kauppila, A. et al. (1997)
Endometrial changes in postmenopausal breast cancer patients
receiving tamoxifen. *Obstet. Gynecol.*, 81,
660–664.
Lindner, D.J. and Borden, E.C. (1997) Effects of
tamoxifen and interferon-beta or the combination on
mammary angiogenesis. *Int. J. Cancer*, 71,
456–461.
exerts antiestrogenic activities through a novel
progesterone receptor A form-mediated mechanism.
Mishell, D.R. Jr (1996) Pharmacokinetics of
depomedroxyprogesterone acetate contraception.
Patriarca, M.T., Sioes, R.D., Smaniottto, S. et al. (1996)
Morphological action of tamoxifen in the
of tamoxifen on bone mineral density measured by
dual-energy x-ray absorptiometry in healthy
Oncol.*, 14, 78–84.
Presta, M. (1988) Sex steroids modulate the synthesis of
basic fibroblast growth factor in human endometrial
denocarcinoma cells: implications for the
vascularization of normal and neoplastic
Endometrial microvascular density during the normal
menstrual cycle and following exposure to long-term
Runic, R., Schatz, F., Krey, L. et al. (1997) Alterations in
endometrial stromal cell tissue factor protein and
mesenger ribonucleic acid expression in patients
experiencing abnormal uterine bleeding while using

Selecto oestrogen receptor modulators

of raloxifene hydrochloride on the endometrium of
postmenopausal women. *Am. J. Obstet. Gynecol.*, 177,
1458–1464.
Boonkasemsanti, W., Reinprayoon, D., Pruksananoda,
on bleeding pattern, hormonal profiles and sex steroid
receptor distribution in the endometrium of Norplant
Charnock-Jones, D.S., Sharkey, A.M., Rajput-Williams,
J. et al. (1993) Identification and localization of
alternately spliced mRNAs for vascular endothelial
growth factor in human uterus and estrogen regulation
in endometrial carcinoma cell lines. *Biol. Reprod.*, 48,
1120–1128.
Cohen, I., Altaras, M.M., Beyth, Y. et al. (1997)
Oestrogen and progesterone receptors in the
endometrium of postmenopausal breast cancer patients
with tamoxifen and progestogens. *Gynecol.
Effects of raloxifene in bone mineral density, serum
cholesterol concentrations, and uterine endometrium
in postmenopausal women. *N. Engl. J. Med.*, 337,
1641–1647.
assessment of treatment of prolonged bleeding in users of
Gagliardi, A. and Collins, D.C. (1993) Inhibition of
angiogenesis by antiestrogens. *Cancer Res.*, 53,
533–535.
Endometrial endothelial cell proliferation in long-term
users of subdermal levonorgestrel. *Hum. Reprod.*, 9,
1647–1651.
Gospodarowicz, D., Ferrara, N., Schweigerer, L. and
Nerfeld, G. (1987) Structural characterization and
biological functions of fibroblast growth factor. *Endocr.
Rev.*, 8, 95–114.
Grow, D.R., Williams, R.F., Hsiu, J.G. and Hodgen, G.D.
(1996) Antiprogestin and/or gonadotropin-releasing
hormone agonist for endometriosis treatment and
Grow, D.R., Reece, M.T., Hsiu, J.G. et al. (1998) Chronic
antiprogestin therapy produces a stable atrophic
dometrium with decreased fibroblast growth factor:
a 1-year primate study on contraception and
Endometrial thickness in tamoxifen-treated patients:
correlation with clinical and pathologic findings. *Am.
Hickey, M., Frasier, I., Dwarte D. *et al.* (1996)
Endometrial vasculature in Norplant users:


