Human Reproduction Update, Vol.13, No.6 pp. 567–580, 2007 doi:10.1093/humupd/dmm023
Advance Access publication July 14, 2007

Progesterone receptor modulators and the endometrium: changes and consequences†

Frances McFarland Horne[1] and Diana L. Blithe[2,3]

[1]Rose Li & Associates, Inc., Bethesda, MD 20817, USA; [2]Contraception and Reproductive Health Branch, Center for Population Research, National Institute of Child Health and Human Development, National Institute of Health, 6100 Executive Boulevard, Room 8B13, Bethesda, MD 20892, USA

[3]Correspondence address. Tel: +301-435-6990; Fax: +301-480-1972; E-mail: blithed@mail.nih.gov

Progesterone receptor modulators (PRMs) have been used for contraceptive research, as well as for treatment of fibroids, endometriosis and heavy or irregular menstrual bleeding. Long-term treatment with these compounds results in changes to the endometrium resulting in potential confusion in trying to characterize endometrial biopsies. A meeting was held to discuss the properties of PRMs, the effects of perturbed hormonal control of the endometrium and the need for further understanding of the biology of progesterone receptor action to facilitate the development of new PRMs. A panel of pathologists was convened to evaluate endometrial changes associated with a minimum of three months of chronic treatment with PRMs. Four different agents were used in the treatment regimens but the pathologists were blinded to treatment regimen or agent. The panel agreed that the endometrial biopsies did not fit into a classification of either proliferative or secretory endometrium but exhibited an unusual architecture that could be characterized as glandular dilatation. There was little evidence of mitosis, consistent with a proposed anti-proliferative effect of PRMs. The panel concluded that the biopsies did not reveal evidence of safety concern and that pathologists and investigators familiar with endometrial effects of chronic PRM exposure should consider working with pharmaceutical companies and regulatory agencies to develop standard descriptions of PRM-associated endometrial changes as well as the types of histologic changes that would signal a need for intervention.

Introduction

Progesterone receptor modulators (PRMs), defined as any molecule that binds the ligand-binding domain of the progesterone receptor (PR), have been used for contraceptive research, as well as treatment of fibroids, endometriosis and heavy or irregular menstrual bleeding. Long-term treatment with these compounds results in changes to the endometrium, but no standard descriptors exist for these changes, and many pathologists are unfamiliar with endometrial changes associated with chronic PRM use. In addition, the mechanisms underlying hormone action on the endometrium, particularly through the PR, are still poorly understood. On 7–8 April 2006, the Center for Population Research at the National Institute of Child Health and Human Development (NICHD), with additional support from the Division of Cancer Treatment and Diagnosis, the Division of Cancer Treatment and the Office of Women's Health of the National Cancer Institute and the National Institutes of Health (NIH) Office of Research on Women's Health, convened a meeting to discuss what is known about the hormonal milieu of the endometrium, the properties of PRMs, the effects of perturbed hormonal control of the endometrium and the need for further understanding of the biology of PR action to facilitate the development of new PRMs. Also discussed were limitations to endometrial assessment and future directions for regulatory interpretation of endometrial changes with chronic PRM treatment. The following summarizes the workshop's deliberations and conclusions.

The endometrium and the menstrual cycle

Estrogen and progesterone are key hormones for steroid action within the endometrial cycle. Following menstruation and repair, the developing ovarian follicle produces estrogen, which promotes endometrial proliferation and stimulates expression of both the estrogen receptor (ER) and the PR across all cell types (Bouchard *et al*., 1991). Much of what is known about the endometrial proliferative phase is based on studies done in non-human primates. During repair and proliferation, mitosis occurs in the functionalis layer of the endometrium (Fig. 1), a highly active layer consisting

†Report of a meeting held in Bethesda, MD, on 7–8 April 2006. The contents of this article reflect both individual and collective opinions of the meeting participants and are not intended to represent the official position of the US Department of Health and Human Services, or the National Institutes of Health; nor are they intended to represent the official positions of any of the meeting cosponsors.

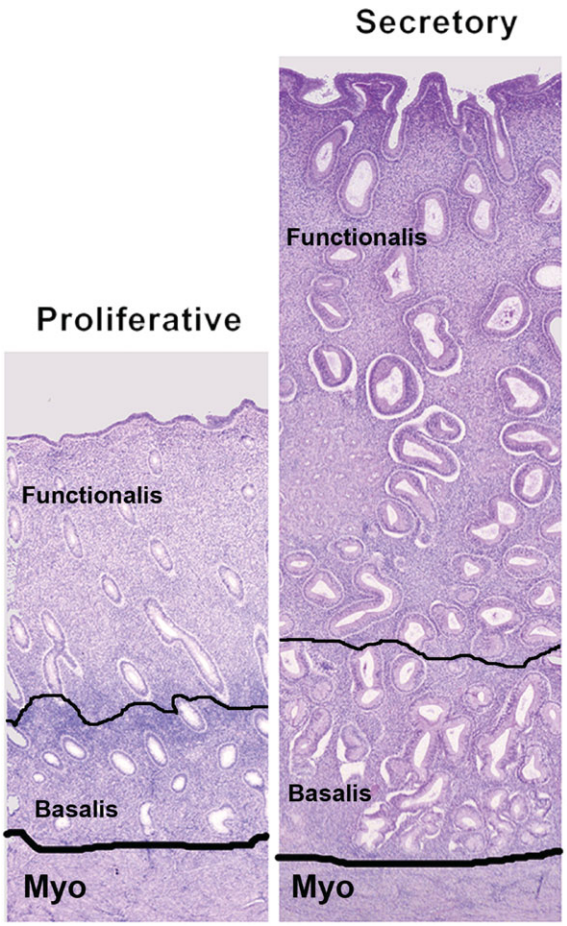

Figure 1: Proliferative and secretory endometrium Representative proliferative or secretory endometria are from cycling cynomolgus macaques (*Macaca fascicularis*). Basalis: stroma and glands of the basalis layer of the endometrium which is largely maintained after menstruation. Functionalis: stroma and glands in the endometrial tissue layer, that is sloughed during menstruation. Myo: myometrium portion of the uterus. Images are courtesy of R.M. Brenner, Oregon National Primate Research Center. Original magnifications ~100×

of glands supported by stroma (McClellan *et al*., 1986; Brenner *et al*., 2003). Results from studies in which bromodeoxyuridine (BrdU) was used to specifically label functionalis or basalis cells (R.M. Brenner and O.D. Slayden, personal communication) demonstrated that the basalis layer may not serve as a source of stem cells for endometrial regeneration after normal menstruation. Instead, changes in the microenvironment may reprogram the few functionalis cells remaining after menstruation to regenerate a new functionalis.

Following ovulation in the human, the corpus luteum produces progesterone which transforms the proliferative endometrium into the secretory structure required for implantation and pregnancy. Mitosis stops in the functionalis layer; in macaques, it begins in the basalis at this time (McClellan *et al*., 1986; Brenner *et al*., 2003). Glands acquire glycogen, which is converted to glycoproteinaceous secretions that support or enhance implantation. Stromal cells undergo predecidualization in which spindle-shaped fibroblasts become plump, epithelia-like cells, and these predecidual cells aggregate in the upper functionalis, forming a compact layer that can receive the embryo. Initial production of progesterone during the ovarian luteal phase occurs in concordance with ER and PR expression in the secretory endometrium. However, expression of both receptors disappears at ~7–10 days after ovulation, corresponding with the usual time of implantation (Wilcox *et al*., 1999). At this point, progesterone acts alone on stromal cells and estrogen production disappears (DeZiegler *et al*., 1998), which is critical for uterine receptivity. The temporal and spatial regulation of the ER and PR is apparent only in the functionalis; PR expression is continuous throughout the cycle in the basalis. In the absence of fertilization, progesterone is eventually withdrawn with the death of the corpus luteum, resulting in the loss of lysosomal integrity (Salamonsen *et al*., 1999). This loss leads to enzymatic degradation of the functionalis, which is cleaved from the basalis and sloughed off in menstrual blood.

Genomic expression patterns in the endometrium can be separated based on steroid receptor patterns and the phase of the menstrual cycle with different effects in the stromal cells or the epithelial cells (Lessey, 2003; Talbi *et al*., 2006). During the proliferative phase, genes involved in the cell cycle, cell signaling and DNA replication are expressed. Genes involved in secretion, ion transport and metabolism are expressed during the early secretory phase, and genes involved in cell adhesion and in the negative regulation of cell division are expressed at middle stages in the secretory phase. The late secretory phase is characterized by the expression of genes required for menstruation.

Consequences of altered steroid action in the endometrium

Endometrial cells require a balance between estrogen and progesterone production. The absence of progesterone removes the 'progesterone brake', leading to persistent estrogenicity and constant endometrial proliferation. The endometrium can become disordered, although the ratio of stroma to glands remains normal, and vascular abnormalities such as dilated capillaries become apparent (Ferenczy and Mutter, 2004).

In women with polycystic ovarian syndrome (PCOS), endometrial ER expression persists into the secretory phase and is high in both the stroma and the lumen, and coactivators are overexpressed (Gregory *et al*., 2002). Androgens also appear to play a role in endometrial physiology. Endometrial expression of the androgen receptor (AR) is higher in women with PCOS than in women with normal endometrium, which putatively contributes to the poor reproductive performance associated with PCOS (Apparao *et al*., 2002).

Women with endometriosis have altered endometrial gene expression patterns compared with women with normal endometria (Giudice, 2003; Kao *et al*., 2003). Cyr61 stimulates adhesion and angiogenesis and its expression is altered in women with endometriosis. In normal endometrium, Cyr61 is expressed in the proliferative phase but disappears by the mid-secretory phase. In women with endometriosis, however, Cyr61 expression persists throughout the cycle potentially contributing to endometriotic lesions (Absenger *et al*., 2004). Anti-estrogen and antiprogestin agents appear to inhibit Cyr61 expression, thus, regulation of Cyr61 is a candidate as a mechanism of action for the therapeutic role for PRMs in the treatment of endometriosis (Sampath *et al*., 2002; Absenger *et al*., 2004).

Steroidal treatment

All cell types within the endometrium, including epithelial, endothelial, stromal, vascular and white cells, appear to respond to progestin treatment. Furthermore, the endometrial effects of progestin treatment derive from the effects of exposure to endogenous steroid production, combined with the consequences of the route through which exogenous steroid is delivered. Some of these differences are based on differences in the down-regulation of the PR and are most likely mediated by the PR-A subtype (Critchley *et al*., 1998b). As demonstrated by an examination of spiral arterioles, the PR is expressed perivascularly (Critchley *et al*., 2001). A recent study indicates that ER-β and PR, but not ER-α, are expressed in the endothelial cells (Krikun *et al*., 2005).

The combined oral contraceptive pill (COCP) provides a systemically administered regimen of ethinyl estradiol (EE) and a progestin. Prolonged use of the COCP results in the replacement of cyclic changes with an atrophic state in which the endometrium is shallow and inactive, with limited regeneration. The proliferative phase is brief, resulting from the inhibitory action of the constituent progestin. In addition, the secretory endometrium lacks the features of the mid- to late luteal phase (Buckley and Fox, 1989), and thin, dilated blood vessels and defects in blood-vessel wall integrity are apparent (Charnock-Jones *et al*., 2000). In a recent study (Anderson *et al*., 2005), the endometrium was atrophic or inactive in two-thirds of COCP users, but no hyperplasia was found.

The levonorgestrel (LNG) intrauterine system (IUS) delivers a high dose of androgenic progestin via a local route of administration but does not inhibit ovulation. Endometrial levels of this progestin are 1000 times higher than that seen with oral or subcutaneous routes of administration. The LNG-IUS has become a popular treatment for heavy bleeding (Anderson and Rybo, 1990). In one study, 64% of women using the LNG-IUS for 6 months canceled their scheduled hysterectomies, compared with 14% of women in the control group (Lahteenmaki *et al*., 1998). In another study (Barrington and Bowen-Simpkins, 1997), 74% of women using the LNG-IUS for 12 months experienced reduced menstrual bleeding within 3 months. In a more recent study, however, Hurskainen and colleagues (2004) found that within 5 years, 42% of women using the LNG-IUS as a treatment for menorrhagia had undergone hysterectomy, suggesting that breakthrough bleeding is still problematic for some women using these types of treatment. Endometrial morphology in women using the LNG-IUS is typical of that observed in women who use progestins long-term, including atrophic glands, decidualized stroma, down-regulation of the ER and PR and changes in blood vessel integrity (Critchley *et al*., 1998a; Ferenczy, 2003). In addition, the AR, which is usually expressed only in the stroma during the proliferative phase and is down-regulated in the late secretory phase, is continuously down-regulated at 3, 6 and 12 months following LNG delivery (Burton *et al*., 2003).

No single factor has been identified to explain the mechanism underlying breakthrough bleeding. It may be that the dilated, superficial and fragile endometrial blood vessels associated with progestin-only contraception might result from alterations in the basement membrane. Another possibility is the role of hypoxia- or reperfusion-induced free radicals in promoting alterations in angiopoietin response (Krikun *et al*., 2002). Yet another possibility is the perturbation of angiogenesis, which is influenced by endocrine and paracrine factors and by hormone manipulation (Lebovic *et al*., 2000). Progesterone increases the expression of the angiogenesis inhibitor, TSP-1 (Mirkin and Archer, 2004), and antiprogestins inhibit it.

Hyperplasia, endometrial polyps and endometrial cancer

Sustained, persistent estrogenic stimulation in the absence of progestin ultimately results in hyperplasia. In the Post-menopausal Estrogen/Progestin Interventions (PEPI, 1996) trial, 60% of women receiving only estrogen had hyperplasia, which was apparent as early as 3–4 months following the initiation of treatment. No increase in hyperplasia was seen with a combination of estrogen and progestin (medroxyprogesterone actetate) versus treatment with a placebo. In another study, hyperplasia was observed in 15% of women receiving unopposed estrogen but in less than 1% of women treated with a combination of estrogen and the progestin, norethindrone acetate (Kurman *et al*., 2000). In one study of women with dysfunctional bleeding, the prevalence of hyperplasia or cancer was 6.8%, and cycle irregularity, hypertension and age were cited as prominent risk factors (Ash *et al*., 1996).

A study of premenopausal women undergoing operative hysteroscopy found a low rate of hyperplasia and no cancer, but a high rate (about 75%) of endometrial polyps (Machtinger *et al*., 2005). The prevalence of endometrial polyps also has been examined in premenopausal women with abnormal bleeding (Farquhar *et al*., 1999; DeWaay *et al*., 2002), perimenopausal women (Goldstein *et al*., 2002), infertile women undergoing IVF (Hinckley and Milki, 2004; Shokeir *et al*., 2004; de Sa Rosa e Silva *et al*., 2005) and a placebo group in a breast cancer trial (Chalas *et al*., 2005). Prevalence varied by study, ranging from 2 to 32%. The most consistent risk factors among these studies were weight of 90 kg or more and age of 40 or 45 years and older. Although endometrial polyps had been reported as precursors for cancer, the prevalence of polyps that did progress to cancer ranged 0–4.5% in studies of premenopausal, perimenopausal and post-menopausal women (Bakour *et al*., 2000; Goldstein *et al*., 2002; Savelli *et al*., 2003; Ben Arie *et al*., 2004; Shushan *et al*., 2004).

Only 10–20% of endometrial cancers occur in premenopausal women (McGEE, 1958; Peterson, 1968; Crissman *et al*., 1981; Gallup and Stock, 1984; Jeffrey *et al*., 1986), and only 2–5% occur in women younger than 40 years (Nisker *et al*., 1978; Jeffrey *et al*., 1986; Gronroos *et al*., 1993). Hyperplasia is of particular concern as a cancer precursor. It is generally agreed that hyperplasia without cytological atypia is not a precursor to cancer. In contrast, several studies have reported endometrial hyperplasia with atypia coincident with carcinoma (Kurman *et al*., 1985; Hunter *et al*., 1994; Widra *et al*., 1995; PEPI Trial Writing Group, 1996; Ho *et al*., 1997; Zaino, 2000; Agostini *et al*., 2001; Valenzuela *et al*., 2003; Novac *et al*., 2005; Shutter and Wright, 2005). The percentage of hyperplasia without atypia progressing to cancer ranged 0.5–4.5%, whereas those with atypia carry a 25% average progression rate to cancer. These studies were mainly done in post-menopausal women. In New Zealand, as guidelines for cancer screening were under development, endometrial samples obtained between 1995 and

1997 from premenopausal women with abnormal uterine bleeding were reassessed (Farquhar *et al*., 1999). Of the 1003 women identified, 4.4% overall had hyperplasia or carcinoma. Prominent risk factors included infertility, nulliparity, weight >90 kg, age >45 years and family history of colon cancer. Family history of endometrial cancer was important only in cases of complex hyperplasia or complex hyperplasia with atypia. On the basis of these reassessments and a calculated probability of progression from hyperplasia to cancer, investigators calculated that 21 women would have to be screened to detect one case of endometrial cancer, if simple hyperplasia cases were included. If screening was limited to complex hyperplasia, 34 women would have to be screened. The New Zealand guidelines thus recommend that among women experiencing heavy bleeding, all women weighing 90 kg or greater and aged 45 years or older should undergo an endometrial evaluation, either by transvaginal ultrasound or EM sampling (http://www.nzgg.org.nz).

Assessing the endometrium

Pathology and histology

The traditional scheme for classifying endometrial biopsies was developed in 1994 by the World Health Organization (WHO) (Scully *et al*., 1994) and is still used in clinical trials, including those evaluated by the US Food and Drug Administration (FDA). This scheme includes four categories categorized by glandular architecture and cytology—simple, hyperplasia without atypia; complex hyperplasia without atypia; simple hyperplasia with atypia and complex hyperplasia with atypia. The presence of atypia is considered a major discriminator for precancerous lesions. The WHO classification scheme is limited by difficulties in assessing endometrial cytology, by poor interobserver reproducibility and by a tendency for pathologists to overdiagnose benign lesions as hyperplasia (Winkler *et al*., 1984; Mutter *et al*., 2000a,b; Zaino, 2000; Wright *et al*., 2002).

Baak and colleagues have devised another classification system based on morphology, morphometry, clonality and immunohistochemistry (Baak *et al*., 2005; Hecht *et al*., 2005). This has led to a clinically predictive diagnosis schema (Table 1), in which endometrial intraepithelial neoplasia (EIN) lesions diagnosed by routine hematoxylin and eosin histology have a 45-fold increased risk for future carcinoma (occurring >1 year after EIN diagnosis). Negative predictive value is very high; 39% of patients with EIN had cancer diagnoses within the first year, compared with 0% of patients for which the diagnosis was benign (not EIN) (Baak *et al*., 2005).

An element of the EIN system is the integration of PTEN inactivation as a marker for malignant potential (Mutter *et al*., 2000a,b). PTEN is a tumor suppressor gene that regulates the rate of cell division and enables apoptosis. Under normal conditions, PTEN expression is robust in an estrogen-rich environment such as the proliferative endometrial glands and stroma. Mutations in PTEN, resulting in PTEN-null cells, are commonly present in cancer cells, including endometrial cancer (Risinger *et al*., 1997). In a study of normal, proliferating endometrial samples, Mutter and colleagues (2001) found that 43% contained glands in which PTEN was absent. These glands were not shed during the menstrual cycle; 83% of women with PTEN-null glands still carried them after 1 year. PTEN-null cells thus would have an advantage in this environment due to resistance to apoptosis. In the presence of progesterone, PTEN levels in normal cells decline, extending their lifespan. The result is that both normal and PTEN-null cells would compete more equally for survival. Hormone action, therefore, can act as a positive or negative selection factor for mutant clones.

However, additional, as yet unknown, changes must occur before these cells become malignant. The diagnosis of EIN is based on histopathologic observations of monoclonal lesions that progressed to carcinoma in individual patients; including evidence that cytology in lesion cells differs from that found in background cells, that the glands in these lesions are not always atypical, and that the absolute appearance of all neoplastic glands is inconsistent among patients. By the time these lesions have expanded into recognizable precancerous aggregates, secondary genetic changes have occurred, the cumulative effect of which is the promotion of aggressive behavior. Thus the transition from premalignancy to malignancy involves a transformation of a benign neoplasm to a malignant one.

The EIN model has several diagnostic implications. Larger-scale topography is important for determining whether lesions are benign, premalignant or malignant. Systemic effects, such as

Table 1: EIN classification

Classification	Characteristics	Recommended treatment
Endometrial hyperplasia	Includes the WHO categories of simple and complex hyperplasia without atypia.	Progesterone therapy or *trans*-abdominal hysterectomy
EIN	EIN lesions are monoclonal as demonstrated by X-chromosome inactivation or clonal propagation of altered microsatellites, and about two-thirds have functional inactivation of PTEN. Defined by five specific diagnostic criteria that are lacking in the WHO schema: (i) cytology that differs between architecturally crowded foci and background; (ii) stromal volume, i.e. <55% of the total endometrium; (iii) maximum linear dimension >1 mm; (iv) exclusion of adenocarcinoma; (v) exclusion of benign mimics.	Like atypical endometrial hyperplasia, EIN would be treated with hormonal therapy or surgery
Adenocarcinoma	Cells have invaded the stroma and myometrium.	Treatment based on surgical stage

EIN, endometrial intraepithelial neoplasia.

those of estrogen on the endometrium, produce changes that are irregular on a small scale but regular throughout the endometrial compartment, whereas premalignancies are monoclonal processes that begin as an expanding localized lesion. It is not atypical cytology, so much as changed cytology between the background and the localized lesion that is critical for diagnosis. Thus, the precancerous EIN is distinguished from endometrial hyperplasia based on molecular and morphometric characteristics. The system eliminates management dilemmas, and inter-observer reproducibility is better than that for the WHO classification system (Baak *et al*., 2005). However, more validation is needed in community practice, and no consensus has yet been reached on the need to change the WHO classification.

Endometrial dating

Because the basalis layer of the human endometrium is less responsive to hormonal stimuli, pathologists do not use this layer to date endometrial biopsies. Noyes criteria (1956, 1963), which were developed based on predictable patterns of morphological characteristics associated with the proliferative phase or the secretory phase of the endometrial cycle, have traditionally been used to date endometrial biopsies. However, work by Lessey and colleagues (2000) suggests that these criteria might be more variable than originally stated, and other studies have questioned the accuracy of these criteria (Coutifaris *et al*., 2004; Myers *et al*., 2004). Inter-observer reproducibility also is problematic for this approach (Myers *et al*., 2004).

The detection and counting of cells undergoing mitosis is the best tool for examining the proliferative endometrium. Traditional S-phase markers such as tritiated thymidine and BrdU have been used to study mitosis in the glands, stroma and endothelium. The Ki67 antibody (Gerdes *et al*., 1983) also has been used extensively and has proven useful for examining patterns of proliferation, but this antibody detects antigen expressed during all phases of the cell cycle and therefore is not specific to cells undergoing mitosis. Likewise, the KiS2 antibody, or p100 (Heidebrecht *et al*., 1997), also detects antigen expressed from S-phase to mitosis, but this antibody is somewhat weaker than that against Ki67. MPM2 (Westendorf *et al*., 1994), which detects several proteins that are phosphorylated during mitosis, is more specific, but it also stains unknown material in the cells. PCNA, which primarily detects proteins associated with DNA synthesis, is another mitotic marker. A recently developed antibody, which detects phosphorylated histone H3, can be used with computer-assisted analysis to improve mitotic counts per gland area (Brenner *et al*., 2003), and the use of this antibody correlates well with traditional mitotic counts in human and macaque endometrium.

Pathologists and histologists are asked to make predictions based on biopsies, which can provide only a snapshot of the endometrium at a certain point in the menstrual cycle, and both face problems with reproducibility and current classifications. Available histological classifications do not account for functional changes such as steroid receptor expression or proliferation markers. In addition, traditional histology has relied on Pipelle sampling, which captures tissue only from the functionalis layer, disrupts the spatial arrangement of tissue, and misses the overall complexity of the endometrium. Furthermore, the lines between endometrial stages are somewhat arbitrary and staging correlates better with the actual LH surge than with defined lengths of preovulatory or postovulatory phases (Johannisson *et al*., 1987). This difficulty may be overcome in the future with the use of genomic analysis and hierarchical clustering classifying endometrial biopsies into stages based on gene expression.

Imaging

Invasive imaging techniques tend to offer more accuracy in assessing the endometrium. Hysteroscopy, e.g. provides a visual inspection of the endometrial epithelium and can aid in identifying structures that impinge upon the endometrium and cause distortions. However, hysteroscopy does not provide information about the biology underlying the observed changes. In addition, invasive techniques carry the risk, although rare, of complications such as perforation, bleeding and infection.

Non-invasive imaging techniques are appealing, but they are limited by the lack of surrogate markers that would allow for the prediction of major health problems. In addition, research based on these methods has been limited to studies in post-menopausal women or in premenopausal women undergoing fertility treatment, and these studies usually have examined only endometrial thickness which does not necessarily correlate with histology. Among available non-invasive techniques, ultrasound has been the most widely used in assessing the endometrium. In a prospective trial in which 77% of the women were premenopausal (Goldchmit *et al*., 1993), ultrasound images appeared to correlate well with endometrial biopsies that were <5 mm thick and showed only benign changes. The 2D ultrasound can distinguish stages in the menstrual cycle based on endometrial thickness and other characteristics, but the homogeneity of the endometrium during the proliferative stage precludes distinct diagnoses. The 3D and saline-infusion sonography (SIS) can be used to evaluate the contours of and further delineate the pathology within the uterine cavity. In addition, 3D ultrasound could be a highly accurate imaging technique from a morphological standpoint.

All available imaging techniques are of varying utility as diagnostic tools. Transvaginal sonography (TVS) and SIS have been useful in diagnosing endometrial polyps in pre- and post-menopausal women, and SIS has aided in the diagnosis of benign conditions in premenopausal women (Dueholm *et al*., 2001; de Kroon *et al*., 2003; Cepni *et al*., 2005). TVS, SIS and hysteroscopy also have been useful in women undergoing endometrial cautery (Dueholm *et al*., 2002) and in identifying lesions in women experiencing heavy bleeding (Critchley *et al*., 2004). Although research on magnetic resonance imaging (MRI) and computed tomography (CT) is limited, MRI has proven useful in diagnosing adenomyosis in premenopausal women (Dueholm *et al*., 2001), and both techniques have been invaluable in detecting cancer (Walsh, 1992; Imaoka *et al*., 1999). CT has proven effective in post-menopausal women, but it has not been studied as a diagnostic tool in premenopausal women.

PRMs in clinical practice

PRMs include mifepristone, onapristone, CDB-2914 and 'J compounds' such as asoprisnil (J867), as well as some others in development (Fig. 2) (Chabbert-Buffet *et al*., 2005).

Mifepristone, which has demonstrated effectiveness as a contraceptive (Gemzell-Danielsson *et al*., 1993), is the most widely

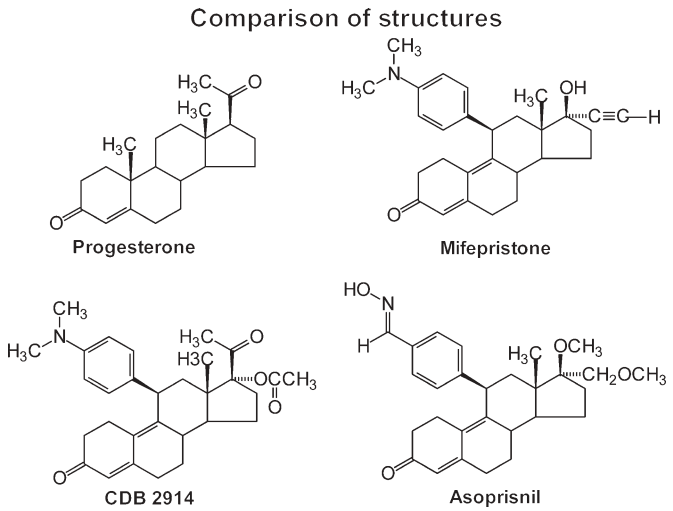

Figure 2: Structures of progesterone and some PRM compounds that are currently in clinical trials for therapeutic indications. Mifepristone—Danco, New York, NY, USA; Exelgyne, Paris, France; CDB-2914—HRA Pharma, Paris, France; Asoprisnil—TAP Pharmaceutical Products, Inc, Lake Forest, IL, USA.

studied of these compounds. Progesterone antagonists, such as mifepristone, do not bind to the ER yet they inhibit endometrial proliferation in women with endogenous estrogen (Brenner *et al*., 2002; Narvekar *et al*., 2004). PRM regulation of steroid receptors in the endometrium has been explored in an effort to explain the effect. Low-dose, chronic administration of mifepristone results in the up-regulation of the ER and AR and the down-regulation of the PR (Narvekar *et al*., 2004). Treatment with a combination of estradiol (E_2) and progesterone antagonists results in the further up-regulation of the ER and PR in the epithelium, expression of the AR in these cells and further up-regulation of all three receptors in the stroma (Brenner *et al*., 2002). Although evidence suggests that androgens may play a role, the antiproliferative effects of PRMs on the endometrium are not fully understood.

Clinical studies of the contraceptive effects of mifepristone have shown varying effects based on dose and duration of use. Low doses of mifepristone (0.1 or 0.5 mg daily) failed to inhibit ovulation (Gemzell-Danielsson *et al*., 1997). In a contraceptive study of the 0.5 mg daily dose, five pregnancies were observed in 32 women over 141 cycles of exposure (Marions *et al*., 1999). Higher daily doses of mifepristone appear to be more effective; in a study of women in Shanghai and Edinburgh who had not used any other contraception, no pregnancies occurred in 200 months of exposure in 50 sexually active women on continuous treatment with 2–5 mg daily (Brown *et al*., 2002). However, 5 mg of mifepristone taken weekly was less effective, with 3 of 18 women becoming pregnant during 63 cycles of treatment (Marions *et al*., 1998). Another study of intermittent mifepristone treatment ended early because of low efficacy; almost half the study participants ovulated monthly, and three pregnancies occurred in 56 women-months Godfrey *et al*., 2004). In other studies, women received 5 or 10 mg mifepristone followed by a progestin; ovulation was inhibited in only 19% of patients at the 5 mg dose and in 24% of patients at the 10 mg dose (Croxatto *et al*., 1996,1998a,b). In a contraceptive trial of sequential mifepristone and progestin, only one pregnancy occurred in 359 women-months of exposure (von Hertzen and Van Look, 2005). Larger studies are needed to confirm the efficacy and safety of sequential treatment.

Uterine fibroids (myoma) are another indication for PRM treatment (Murphy *et al*., 1993; Zeng *et al*., 1998; Steinauer *et al*., 2004; Chwalisz *et al*., 2005a,b; Eisinger *et al*., 2005). In clinical trials of mifepristone that were not placebo controlled, 5–50 mg daily for 3–6 months reduced myoma volumes by 26–74%, with a rate of amenorrhea ranging from 63 to 100%. In addition, mifepristone treatment reduced the prevalence of dysmenorrhea, menorrhagia and pelvic pressure in these trials. A study by Eisinger *et al*. (2005) also showed a 50% reduction in uterine and myoma volume, with amenorrhea occurring in 60–65% of participants receiving mifepristone. Asoprisnil also has been studied for its efficacy in treating fibroids and has shown dose-dependent effects on uterine volume reduction, myoma volume, pressure symptoms, duration and intensity of bleeding, menorrhagia and amenorrhea (Chwalisz *et al*., 2005a,b). When mifepristone treatment was stopped in a Chinese population, fibroids recurred at a rate of 18%, compared with a rate of 40% in women who had received GnRH receptor agonist (Zeng *et al*., 1998). Another study of response to treatment cessation showed that in women who had received 5–10 mg mifepristone daily for 12 months, uterine volumes were considerably less at 10 months after treatment ended than they were at baseline (Eisinger *et al*., 2005).

Other indications for treatment with PRMs include endometriosis, prolonged menstrual bleeding, infertility and cancer. Daily mifepristone treatment for 3–6 months, at 50 mg per day, alleviated endometriosis, resulting in amenorrhea, pain reduction and no effects on bone mineral density (Kettel *et al*., 1996; Chwalisz *et al*., 2005a,b).

A major side effect leading to discontinuation during the first few months of use of progestin-only contraceptives is prolonged bleeding. Mifepristone improved the bleeding patterns in women with LNG-releasing devices, progestin-only pills or Depo-Provera® (Cheng *et al*., 2000; Gemzell-Danielsson et al., 2002; Jain *et al*., 2003; Massai *et al*., 2004; Weisberg *et al*., 2006); addition of EE along with mifepristone resulted in further improvement (Weisberg *et al*., 2006). In this latter study, doxycycline (a potent inhibitor of matrix metalloproteinases) was as effective as the combination of mifepristone and EE in improving the bleeding patterns of Implanon™ users.

After oral administration, mifepristone has been detected in follicular fluid (Cekan *et al*., 1989) and has been shown to inhibit premature LH surges (Escudero *et al*., 2005). By retarding endometrial maturation, mifepristone might shift the time of implantation, resulting in improved synchronization of embryonic and endometrial maturation and increased pregnancy rates (Paulson *et al*., 1997; Escudero *et al*., 2005).

The anti-tumor effects of PRMs have been studied in postmenopausal women with metastatic breast cancer and in women with refractory ovarian cancer (Perrault *et al*., 1996; Rocereto *et al*., 2000). Mifepristone has proven somewhat effective in the treatment of meningioma, although associated side effects of high-dose chronic therapy of mifepristone may be problematic in some cases (Spitz *et al*., 2005; Grunberg *et al*., 2006). Newer generations of PRMs with reduced antiglucocorticoid activity may be better tolerated for chronic therapy in which effects on the glucocorticoid receptor (GR) are not beneficial.

PRMs and the endometrium

Clinical observations

PRMs exert dose-dependent effects on both the endometrium and ovulation. A potential concern about continuous daily treatment with a progesterone antagonist is that the endometrium would be chronically stimulated by estrogen (unopposed estrogen), leading to development of endometrial cancer. Importantly, chronic treatment with various PRMs did not result in endometrium exhibiting an unopposed estrogen effect, which would be characterized by the prevalence of mitotic activity and the absence of apoptosis.

Studies of <2 mg mifepristone daily demonstrated normal or disordered endometrium and normal or delayed ovulation (Batista *et al*., 1992; Gemzell-Danielsson *et al*., 1997; Croxatto *et al*., 1998a,b; Marions *et al*., 1999). At daily doses between 2 and 10 mg, however, the endometrium exhibited more disordered architecture, including cystic glandular dilatation, decreased mitotic activity and a non-secretory glandular pattern (Ledger *et al*., 1992; Croxatto *et al*., 1993; Cameron *et al*., 1995; Baird *et al*., 2003; Narvekar *et al*., 2004). In the study of 2 or 5 mg daily mifepristone treatment in women in Shanghai and Edinburgh (Narvekar *et al*., 2004), endometrial thickness had increased by 4 months of mifepristone treatment in the women in Edinburgh but decreased in the women in Shanghai, with some ethnic differences in histology. Ovulation was inhibited in 95% of women taking daily doses of 5 mg in this study. Further study of these populations found ethnic differences in estrogen secretion, with greater suppression in the Chinese women. In a study using a higher dose of mifepristone, women receiving 50 mg mifepristone daily for 6 months showed suppressed follicular development and a mixture of secretory and proliferative endometrium. Mitosis was decreased, and the ER and PR were strongly expressed in the glands and stroma (Murphy *et al*., 1995).

Safety concerns surrounding PRM treatment have centered on possible associations with endometrial hyperplasia. Eisinger and colleagues reported simple hyperplasia after 6 months of treatment in 14% of women receiving mifepristone for uterine myomas; all these women had been taking 10 mg daily (Chwalisz *et al*., 2005a,b). It should be noted, however, that many of the hyperplasias reported in this study were actually cystic glandular dilatation. In an earlier study, this group reported that simple hyperplasia had occurred in 28% of women taking 5–10 mg daily (Eisinger *et al*., 2003). Inactive endometria and/or cystic glandular dilatation were apparent in women taking 2–5 mg daily; in one case, simple hyperplasia without atypia observed at 60 days reverted to atrophic endometrium at 120 days (Baird *et al*., 2003). No hyperplasia was observed in women taking 1 mg daily, although 25% of these women experienced increased endometrial thickness, and 34% experienced dilated glands (Croxatto *et al*., 1998a,b).

At very high doses of mifepristone, both antiprogestin and antiglucocorticoid effects are observed. The GR is expressed throughout the menstrual cycle, in decidua, and in white cells, both in the endometrial stroma and in the endothelium (Henderson *et al*., 2003). Chronic administration of low-dose mifepristone results in pronounced expression of the GR in the glands (Narvekar *et al*., 2006). In one case report, a woman with Cushingoid features and morbid osteoporosis, who received 400 mg mifepristone daily to stop further bone loss, experienced complex hyperplasia that resolved to normal once treatment was discontinued (Newfield *et al*., 2001). Across several studies, in a total of 76 meningioma patients with treatment periods ranging from 10 months to 14 years of daily doses (about 200 mg) of mifepristone, 14% had hyperplasia, 8% had hyperplasia combined with endometrial polyps and 2.6% had endometrial polyps alone (Martineau and Levental, 2000; Spitz *et al*., 2005; Grunberg *et al*., 2006). At these doses, the antiglucocorticoid activity of mifepristone increases cortisol and adrenocorticotrophic hormone levels, which in turn lead to increased production of E_2 precursors (Nieman *et al*., 1985; Zeng *et al*., 1998; Kettel *et al*., 1996; Martineau and Levental, 2000; Newfield *et al*., 2001). The antiglucocorticoid properties of mifepristone have provided a rationale for its use to treat neuropsychiatric disorders associated with abnormalities in the hypothalamic–pituitary axis (Wolkowitz and Reus, 1999; Belanoff *et al*., 2002; Pomara *et al*., 2002; Young *et al*., 2004; Simpson *et al*., 2005; Flores *et al*., 2006). Mifepristone has been used successfully to treat psychotic and bipolar depression and is under evaluation for treatment of schizophrenia and Alzheimer's disease. Daily asoprisnil treatment, on the other hand, has shown no effect on cortisol levels (DeManno *et al*., 2003; Chwalisz *et al*., 2005a,b). Also, it should be emphasized that low doses of mifepristone, which are proposed for benign gynecological complaints, have not been associated with complex hyperplasia.

Classification of PRM treated endometrium

Most of the studies relied on endometrial biopsies sampled once during the treatment period, and consideration of PRM effects should take into account the hormonal milieu of the endometrium at the time of sampling. Although several changes have been identified in endometrial samples from women receiving PRM treatment, descriptions of these changes do not fit into the current lexicon for histology or pathology, and no common labels have been devised. At present, how these samples are diagnosed depends largely on the pathologist's experience in examining PRM-treated endometrial tissue, the kinds of questions the pathologist is asked, and the descriptors listed on the institution's report form.

For the purpose of better understanding the challenges facing the pathologists who will be called upon to diagnose endometrial effects of chronic PRM treatment, the organizers of the meeting invited a panel of pathologists with expertise in reading endometrial biopsies. The pathologists reviewed slides of biopsies obtained after PRM treatment for at least three months. Four different agents were used in the treatment regimens, but the pathologists were unaware of which agent had been used for any particular slide. After examining the slides, the panel agreed that the biopsies exhibited an unusual architecture that could be characterized as demonstrating glandular dilatation (Fig. 3). There was little evidence of mitosis, consistent with the proposed antiproliferative effect of PRMs. The group concluded that the endometrial samples did not fit into a classification of either proliferative or secretory endometrium. In the absence of an opportunity to describe what was seen (i.e. using a form with pre-existing categories), or

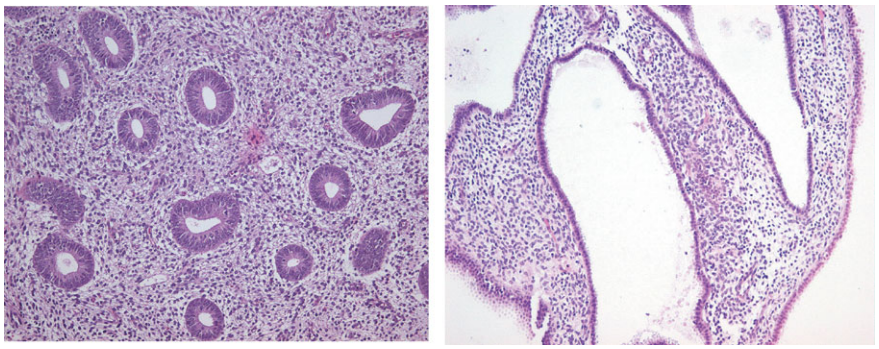

Figure 3: Endometrium obtained by endometrial biopsy Proliferative endometrium was obtained during the follicular phase of the menstrual cycle. PRM treated endometrial tissue was obtained after daily treatment for 3 months with a PRM. The figure is representative of images seen when any of four different PRM compounds were used as the treatment agent. Original magnifications ~100×. Images courtesy of C. Bergeron, Laboratoire Pasteur-Cerba and A.R.W. Williams, University of Edinburgh

experience with looking at many slides showing the same characteristics, the pathologists agreed that there would be a tendency to overdiagnose hyperplasia resulting from prolonged PRM treatment. After reviewing many slides, however, the panel concluded that the biopsies did not reveal evidence of safety concern. More study will be needed to identify long-term outcomes of PRM treatment, rather than relying on pathologists and histologists to extrapolate information from biopsies obtained after a short period of PRM exposure.

Few studies have used ultrasound or other imaging techniques to assess endometrial changes following PRM treatment, and the few that have done so focus primarily on endometrial thinning. The effects of compounds such as danazol and goserelin acetate (Garry *et al*., 1996), oral contraceptives (Grow and Iromloo, 2006) and tamoxifen (Chang *et al*., 1998) have been examined in greater detail. The results from placebo-controlled studies using ultrasound to examine the effects of selective ER modulators (SERMs) in post-menopausal women suggest that these compounds, though estrogenic, do not stimulate endometrial proliferation (Voipio *et al*., 2002; Ronkin *et al*., 2005). Ultrasound evaluation in premenopausal women has been used primarily for those women undergoing fertility treatment and has suggested a correlation between endometrial thickness and pregnancy outcome (Kovacs *et al*., 2003; Al Fozan *et al*., 2004). For future research studies, TVS and SIS might be most useful in premenopausal women, whereas SIS and hysteroscopy might prove more useful for post-menopausal women. MRI and CT, though effective in revealing neoplasia, would not be useful for the types of studies needed to assess the effects of PRMs on the endometrium.

PRMs: design and selectivity

Ideally, selective PRMs (SPRMs) would offer high affinity, minimal steroid receptor cross-reactivity, either agonistic or antagonistic action in the uterus (depending on the indication), neutral or antagonistic action in the breast and no activity in the central nervous system, cardiovascular system or liver. Yet the rational design of such a compound faces several limitations. The definitions of progestin versus antiprogestin vary across studies, depending on the end points those studies use. Distinguishing between the two classes based on estrogen activity can be problematic. Both progestins and antiprogestins have been shown to function similarly in the breast, e.g. in the regulation of the estrogen-induced pS2 protein (Savoldi *et al*., 1995). In addition, the mechanism of PR action is poorly understood for any tissue, and the contribution of genomic and non-genomic activities to PR biology is unknown. Traditional models for PR action have emphasized the PR-B isoform as the one through which downstream activation takes place (Leslie *et al*., 1997). However, emerging evidence suggests that the PR-A and PR-B isoforms regulate different genes (Cheng *et al*., 2001; An *et al*., 2005; Smid-Koopman *et al*., 2005), and studies in mice have demonstrated that the PR-A isoform mediates the anti-estrogenic activities of progestins (Fernandez-Valdivia *et al*., 2005).

Steroid receptor cofactors also must be considered. Work with SERMs indicates that the selectivity of the steroid receptor results in part from the receptor's interaction with different coactivators (McDonnell *et al*., 2000; Hall and McDonnell, 2005). There are >200 coactivators, whose expression patterns differ among cell types, and the structure of the receptor can adapt various conformations to allow different protein-protein interactions. The rational design of SPRMs will depend on the identification of cofactors for the PR and ways to regulate their activity. The use of phage display to identify potential AR cofactors (Hsu *et al*., 2003) may serve as a model for SPRM discovery. Almost 400 proteins were found, 20% of which were transcription factors. Computer-assisted hierarchical clustering was used to group putative ligands based on their relative binding affinities for various cofactors, and the anabolic and proliferative activities of the AR could be separated based on cofactor interactions. Work to identify PR-cofactor interactions and the ligand dependence for those interactions can further enable drug discovery.

PRMs: pharmacodynamic properties

Existing PRMs all bind the PR binding pocket, but with varying affinity. The binding affinity does not necessarily predict the effects of that compound. For example, onapristone is among the most potent progesterone antagonists, but it binds the PR with low affinity. Whereas onapristone shows a complete absence of PR-agonist properties with respect to morphological and functional aspects within the genital tract, other PRMs, including mifepristone, clearly show both PR-agonistic and -antagonistic effects. Furthermore, the effects exerted by these compounds

depend on the hormonal background, such as pregnancy, the presence or absence of progesterone or research designs in ovariectomized animals given exogenous estrogen.

Studies in rabbits and guinea pigs suggest that the pharmacological effects of these compounds arise from interactions between antagonistic and agonistic properties (Elger *et al*., 2000). The compounds tested in these studies varied in the degrees of antagonistic and agonistic effects on ovulation, endometrial proliferation and labor induction. Some compounds that show pronounced PR-agonistic effects on vaginal and uterine mucosa have a blunted or abolished potential to induce labor in pregnant guinea pigs, irrespective of the tested dosage. Above certain dose levels, a balance of antagonistic and agonistic properties appears to prevail and results in a plateau of the dose-response curve, below the respective maximum of agonists, such as progesterone, or antagonists, such as onapristone. Even mifepristone, often considered a 'pure' antagonist, appears to have a balance of both antagonistic and agonistic properties. In humans, mifepristone or onapristone exhibit antagonistic effects in inducing bleeding (Herrmann *et al*., 1982), preventing secretory endometrium formation and ER and PR suppression (Swahn *et al*., 1990; Cameron *et al*., 1996) and inhibiting progesterone-induced gene expression (Cameron *et al*., 1997). The AR also is upregulated in response to antagonistic effects (Gemzell-Danielsson *et al*., 1993; Chabbert-Buffet *et al*., 2005). However, mifepristone also exhibits agonistic effects by inducing secretory changes in estrogen-treated, post-menopausal endometrium (Gravanis *et al*., 1985; Koering *et al*., 1986) by suppressing FSH and LH production (Herrmann *et al*., 1982; Batista *et al*., 1994; Baird *et al*., 1995).

The balance between the antagonistic and agonistic properties of these compounds has therapeutic implications. Submaximal antagonistic effects of some PRMs cannot be overcome by merely changing the dose. Inhibitory effects on ovulation are apparent with both PR antagonists and agonists, but the combination of these activities may lead to an abolishment of anti-ovulatory activity, as shown in guinea pig (Chwalisz *et al*., 2000; Elger *et al*., 2000; Schubert *et al*., 2005). A pharmacodynamic or functional definition of an ideal SPRM may include the presence of significant PR-agonist or antagonist properties, the absence of unopposed estrogenic effects in the endometrium and the control of endometrial proliferation and inhibition of menstrual bleeding, irrespective of effects on ovulation.

PRM development: regulatory considerations

Europe: CHMP, European Medicines Agency

In the European Union, there is no formal regulatory guidance for PRMs or for usage in premenopausal women. However, the committee for Medical Products for Human Use (CHMP) has issued points to consider for hormone replacement therapy (HRT) in post-menopausal women (www.emea.eu.int/pdfs/human/ewp/002197en.pdf), which call for HRT regimens to include a combination of estrogen and progestin to prevent the estrogen-associated increase in risk for endometrial cancer. These guidelines rely on standard histological classifications and call for the assessment of efficacy and safety by obtaining biopsies at baseline, the end of a study and the end of treatment. Biopsies must be obtained by independent pathologists who are blinded to treatment and the assessment point at which the biopsy is obtained, and samples must be processed in a central laboratory. The threshold for safety is an incidence rate of $<2\%$ for endometrial cancer after 1 year of treatment, with an upper limit of a two-sided 95% confidence interval (CI) of 2% or less.

The CHMP also has issued guidance on hormonal contraceptives, but, with the exception of an indirect assessment through bleeding patterns, no specific recommendations regarding endometrial safety have been included in the safety section of this guideline. However, recommendations for clinical and pharmacological assessment include studies of hormonal activity and the mechanism of contraception. If there is any indication that endometrial safety is compromised, thorough clinical safety documentation is required, including endometrial biopsies when needed to rule out malignant transformation. In the absence of validation, surrogate endpoints cannot replace endometrial biopsy. The CHMP guidance on hormonal contraceptives also refers to International Conference of Harmonization (ICH) Topic E1 guidance, which addresses the extent of population exposures in the assessment of clinical safety for drugs that will be used long-term to treat non-life-threatening conditions (www.emea.eu.int/pdfs/human/ich/037595en.pdf). Topic E1 defines 'long-term' as chronic or repeated intermittent use for longer than 6 months, and it calls for safety evaluations to characterize and quantify the safety of a drug over a duration of time consistent with long-term use.

United States: FDA

Like the CHMP, the FDA has no formal guidance on steroid receptor modulators. The guidance, that is relevant to the effects of steroid receptor modulators on the endometrium is the document titled 'Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms—Recommendations for Clinical Evaluation' (www.fda.gov/cder/guidance/5412dft.pdf). These guidelines, which are targeted toward treatment in post-menopausal women, call for endometrial evaluation via biopsies taken at baseline, during treatment and at 1 year after treatment. Sonography is encouraged for adjunct assessment. The guidelines require histological assessment by three independent pathologists who are blinded both to treatment and to the readings of the other reviewing pathologists. The final diagnosis for a sample is based on concurrence by at least two of the reviewers or, in the case of no agreement, the most serious diagnosis. Thus, overdiagnosis can sometimes be problematic. The safety threshold for new treatments is an incidence rate of 1% or less for endometrial hyperplasia, with the upper bound of a one-sided, 95% CI of 4% or less. Histological assessments rely on standard WHO criteria.

More studies are needed before the FDA can establish guidelines for development of PRMs for therapeutic indications. The effects of PRM treatment on the endometrium and key regulatory questions will center on risk and benefit of new compounds compared with the known risks of available treatments. The development of new guidance most likely would consider preclinical findings, known pharmacological effects, indications and duration of treatment, and attention would be paid toward the use of songoraphy and surrogate markers such as PTEN during

safety assessments. In addition, because of the antagonistic and agonistic properties apparent in PRMs, continued safety testing might be required. Education also would be important to ensure standardized diagnoses, particularly among pathologists who are not familiar with endometrial changes associated with PRM treatment.

The requirement for concurrence by three independent pathologists is of some concern, particularly if reviewers are unfamiliar with PRM-associated changes and in light of the potential bias introduced by groups. This concern can be addressed at earlier stages of PRM development, when pathologists can work together to develop standard descriptors for PRM-associated changes. However, the opinions of three independent pathologists would still be required during Phase III confirmatory trials.

Future directions

Further understanding of the biology of PR action is needed to facilitate the development of new PRMs. Specifically, the contribution of cofactors to the balance between estrogen and progesterone during the menstrual cycle, and the role of growth factors should be explored. The development of receptor isoform-specific PRMs might prove beneficial, in light of differences in isoform expression among various types of malignancies (Arnett-Mansfield *et al*., 2001; Mote *et al*., 2002; McGowan *et al*., 2004; Mote *et al*., 2004). How the antiglucocorticoid properties of PRMs can be exploited to treat malignancies also should be explored, particularly in light of *in vitro* studies demonstrating high-affinity GRs in malignancies that are not normally hormone dependent (Alford *et al*., 1979; Walker *et al*., 1980).

The need for standard classifications is an important theme for PRM development and the effects of these compounds on the endometrium. Two classification schemes based on pharmacodynamic properties (Chwalisz *et al*., 2005a,b) and interactions with coregulators (Smith and O'Malley, 2004) have been proposed. New and standardized nomenclature should be developed to address not only the interaction between antagonistic and agonistic properties and the role for receptor cofactors, but also the combination of endometrial and ovulatory effects induced by PRMs. Consensus also is needed on histological and pathological classifications. Histologists and pathologists should work together to develop consistent, standardized terms to describe hyperplasia, precancerous lesions and endometrial stages during the menstrual cycle. In addition, pathologists familiar with endometrial effects of chronic PRM exposure should consider working with pharmaceutical companies and involving regulatory agencies to develop standard descriptions of PRM-associated endometrial changes and to educate all pathologists to adopt these standard terms.

Investigators also should work with regulatory agencies to consider modifications of existing guidelines for short-term use of PRMs, including how to examine ethnic or geographic data, if data are pooled, and ways to extrapolate recommendations for post-menopausal women to perimenopasual and premenopausal women. Consensus also must be reached on acceptable monitoring for PRM development, particularly the type and duration of monitoring, as well as on the types of histologic changes that would signal a need for intervention.

Acknowledgements

The Organizing Committee gratefully acknowledges the companies that generously provided slides from their clinical studies for the pathology review panel. Mifepristone—Danco, New York, NY, and the University of Rochester, Rochester, NY, USA, University of Edinburgh, Edinburgh, UK; CDB-2914—HRA Pharma, Paris, France; Johnson and Johnson Research and Development, LLC, Raritan, NJ, USA; and Asoprisnil—TAP Pharmaceutical Products, Inc, Lake Forest, IL, USA.

Appendix

Meeting organizers

Diana Blithe, National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, MD, USA.

David Baird, University of Edinburgh, Edinburgh, Scotland.

Philippe Bouchard, Hospital Saint Antoine, Paris, France.

Vivian Brache, PROFAMILIA, Santa Domingo, Dominican Republic.

Horacio Croxatto, Instituto Chileno de Medicina Reproductiva, Santiago, Chile.

Ian Fraser, University of Sydney, Sydney, Austrailia.

Regine Sitruk-Ware, Population Council and Rockefeller University, New York, NY USA.

Edward Trimble, National Cancer Institute, NIH, Bethesda, MD, USA.

Speakers

David Archer, CONRAD Clinical Research Center, Norfolk, VA, USA.

David Baird, University of Edinburgh, Edinburgh, Scotland.

Robert Brenner, Oregon National Primate Research Center, Beaverton, OR, USA.

Hilary Critchley, University of Edinburgh, Edinburgh, Scotland.

Walter Elger, EnTec GmbH, Berlin,Germany.

Cindy Farquhar, University of Auckland, Auckland, New Zealand.

Alex Ferenczy, McGill University, Montreal, Quebec, Canada.

Bruce A. Lessey, University of North Carolina, Chapel Hill, NC, USA.

Donald McDonnell, Duke University, Durham, NC, USA.

Scott Monroe, Food and Drug Administration, Silver Spring, MD, USA.

George Mutter, Harvard Medical School, Boston, MA, USA.

Lisa Rarick, Reproductive Health and Regulatory Affairs, Gaithersburg, MD, USA.

Irving Spitz, Ben Gurion University of the Negev, Israel.

Elizabeth van Vlijmen, Dutch Medical Evaluation Board, The Hague, The Netherlands.

Alistair R.W. Williams, University of Edinburgh, Edinburgh, Scotland.

Pathology review panel

Christine Bergeron, Laboratoire Pasteur-Cerba, Cergy Pontoise, France.

Liane Deligdisch, The Mount Sinai School of Medicine, New York, NY, USA.

Alex Ferenczy, McGill University, Montreal, Quebec, Canada.

Michael Glant, DCL Medical Laboratories, Inc, Indianapolis, IN, USA.

Maria Merino, National Cancer Institute, NIH, Bethesda, MD, USA.

George Mutter, Harvard Medical School, Boston, MA, USA.

Alistair Williams, Royal Infirmary of Edinburgh, Edinburgh, Scotland.

Reference

Absenger Y, Hess-Stumpp H, Kreft B, Kratzschmar J, Haendler B, Schutze N, Regidor PA, Winterhager E. Cyr61, a deregulated gene in endometriosis. *Mol Hum Reprod* 2004;**10**:399–407.

Agostini A, Cravello L, Bretelle F, Demaisonneuve AS, Roger V, Blanc B. Risk of discovering endometrial carcinoma or atypical hyperplasia during hysteroscopic surgery in postmenopausal women. *J Am Assoc Gynecol Laparosc* 2001;**8**:533–535.

Al Fozan H, Al Khadouri M, Tan SL, Tulandi T. A randomized trial of letrozole versus clomiphene citrate in women undergoing superovulation. *Fertil Steril* 2004;**82**:1561–1563.

Alford TC, Do HM, Geelhoed GW, Tsangaris NT, Lippman ME. Steroid hormone receptors in human colon cancers. *Cancer* 1979;**43**:980–984.

An BS, Choi JH, Choi KC, Leung PC. Differential role of progesterone receptor isoforms in the transcriptional regulation of human gonadotropin-releasing hormone I (GnRH I) receptor, GnRH I, and GnRH II. *J Clin Endocrinol Metab* 2005;**90**:1106–1113.

Anderson FD, Hait H, Hsiu J, Thompson-Graves AL, Wilborn WH, Williams RF. Endometrial microstructure after long-term use of a 91-day extended-cycle oral contraceptive regimen. *Contraception* 2005;**71**: 55–59.

Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990;**97**:690–694.

Apparao KB, Lovely LP, Gui Y, Lininger RA, Lessey BA. Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome. *Biol Reprod* 2002;**66**:297–304.

Arnett-Mansfield RL, deFazio A, Wain GV, Jaworski RC, Byth K, Mote PA, Clarke CL. Relative expression of progesterone receptors A and B in endometrioid cancers of the endometrium. *Cancer Res* 2001;**61**:4576–4582.

Ash SJ, Farrell SA, Flowerdew G. Endometrial biopsy in DUB. *J Reprod Med* 1996;**41**:892–896.

Baak JP, Mutter GL, Robboy S, van Diest PJ, Uyterlinde AM, Orbo A, Palazzo J, Fiane B, Lovslett K, Burger *et al*. The molecular genetics and morphometry-based endometrial intraepithelial neoplasia classification system predicts disease progression in endometrial hyperplasia more accurately than the 1994 World Health Organization classification system. *Cancer* 2005;**103**:2304–2312.

Baird DT, Thong KJ, Hall C, Cameron ST. Failure of oestrogen induced luteinizing hormone surge in women treated with mifepristone (RU 486) every day for 30 days. *Hum Reprod* 1995;**10**:2270–2276.

Baird DT, Brown A, Critchley HO, Williams AR, Lin S, Cheng L. Effect of long-term treatment with low-dose mifepristone on the endometrium. *Hum Reprod* 2003;**18**:61–68.

Bakour SH, Khan KS, Gupta JK. The risk of premalignant and malignant pathology in endometrial polyps. *Acta Obstet Gynecol Scand* 2000;**79**:317–320.

Barrington JW, Bowen-Simpkins P. The levonorgestrel intrauterine system in the management of menorrhagia. *Br J Obstet Gynaecol* 1997;**104**:614–616.

Batista MC, Cartledge TP, Zellmer AW, Merino MJ, Axiotis C, Loriaux DL, Nieman LK. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: a potential new contraceptive strategy. *Am J Obstet Gynecol* 1992;**167**:60–65.

Batista MC, Cartledge TP, Zellmer AW, Nieman LK, Loriaux DL, Merriam GR. The antiprogestin RU486 delays the midcycle gonadotropin surge and ovulation in gonadotropin-releasing hormone-induced cycles. *Fertil Steril* 1994;**62**:28–34.

Belanoff JK, Rothschild AJ, Cassidy F, DeBattista C, Baulieu EE, Schold C, Schatzberg AF *et al*. An open label trial of C-1073 (mifepristone) for psychotic major depression. *Biol Psychiatry* 2002;**52**:386–392.

Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, Dgani R, Hagay Z. The malignant potential of endometrial polyps. *Eur J Obstet Gynecol Reprod Biol* 2004;**115**:206–210.

Bouchard P, Marraoui J, Massai MR, Medalie DA, DeZiegler D, Perrot-Applanat M, Frydman R, Bergeron C. Immunocytochemical localization of oestradiol and progesterone receptors in human endometrium: a tool to assess endometrial maturation. *Baillieres Clin Obstet Gynaecol* 1991;**5**:107–115.

Brenner RM, Slayden OD, Critchley HO. Anti-proliferative effects of progesterone antagonists in the primate endometrium: a potential role for the androgen receptor. *Reproduction* 2002;**124**:167–172.

Brenner RM, Slayden OD, Rodgers WH, Critchley HO, Carroll R, Nie XJ, Mah K. Immunocytochemical assessment of mitotic activity with an antibody to phosphorylated histone H3 in the macaque and human endometrium. *Hum Reprod* 2003;**18**:1185–1193.

Brown A, Cheng L, Lin S, Baird DT. Daily low-dose mifepristone has contraceptive potential by suppressing ovulation and menstruation: a double-blind randomized control trial of 2 and 5 mg per day for 120 days. *J Clin Endocrinol Metab* 2002;**87**:63–70.

Buckley CH, Fox H. The normal endometrium as seen in biopsy material. In: Buckley CH (ed). *Biopsy Pathology of the Endometrium.* London: Chapman and HallLondon, 1989, 30–47.

Burton KA, Henderson TA, Hillier SG, Mason JI, Habib F, Brenner RM, Critchley HO. Local levonorgestrel regulation of androgen receptor and 17beta-hydroxysteroid dehydrogenase type 2 expression in human endometrium. *Hum Reprod* 2003;**18**:2610–2617.

Cameron ST, Critchley HO, Buckley CH, Chard T, Kelly RW, Baird DT. The effects of post-ovulatory administration of onapristone on the development of a secretory endometrium. *Hum Reprod* 1996;**11**:40–49.

Cameron ST, Critchley HO, Buckley CH, Kelly RW, Baird DT. Effect of two antiprogestins (mifepristone and onapristone) on endometrial factors of potential importance for implantation. *Fertil Steril* 1997;**67**:1046–1053.

Cameron ST, Thong KJ, Baird DT. Effect of daily low dose mifepristone on the ovarian cycle and on dynamics of follicle growth. *Clin Endocrinol (Oxf)* 1995;**43**:407–414.

Cekan S, Aedo AR, Segersteen E, Van Look P, Messinis I, Templeton A. Levels of the antiprogestin RU 486 and its metabolites in human blood and follicular fluid following oral administration of a single dose. *Hum Reprod* 1989;**4**:131–135.

Cepni I, Ocal P, Erkan S, Saricali FS, Akbas H, Demirkiran F, Idil M, Bese T. Comparison of transvaginal sonography, saline infusion sonography and hysteroscopy in the evaluation of uterine cavity pathologies. *Aust N Z J Obstet Gynaecol* 2005;**45**:30–35.

Chabbert-Buffet N, Meduri G, Bouchard P, Spitz IM. Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. *Hum Reprod Update* 2005;**11**:293–307.

Chalas E, Costantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, Runowicz CD. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. *Am J Obstet Gynecol* 2005;**192**:1230–1237.

Chang J, Powles TJ, Ashley SE, Iveson T, Gregory RK, Dowsett M. Variation in endometrial thickening in women with amenorrhea on tamoxifen. *Breast Cancer Res Treat* 1998;**48**:81–85.

Charnock-Jones DS, Macpherson AM, Archer DF, Leslie S, Makkink WK, Sharkey AM, Smith SK. The effect of progestins on vascular endothelial growth factor, oestrogen receptor and progesterone receptor immunoreactivity and endothelial cell density in human endometrium. *Hum Reprod* 2000;**15**(Suppl 3):85–95.

Cheng KW, Cheng CK, Leung PC. Differential role of PR-A and -B isoforms in transcription regulation of human GnRH receptor gene. *Mol Endocrinol* 2001;**15**:2078–2092.

Cheng L, Zhu H, Wang A, Ren F, Chen J, Glasier A. Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel. *Hum Reprod* 2000;**15**:1969–1972.

Chwalisz K, Brenner RM, Fuhrmann UU, Hess-Stumpp H, Elger W. Antiproliferative effects of progesterone antagonists and progesterone receptor modulators on the endometrium. *Steroids* 2000;**65**:741–751.

Chwalisz K, Elger W, Stickler T, Mattia-Goldberg C, Larsen L. The effects of 1-month administration of asoprisnil (J867), a selective progesterone receptor modulator, in healthy premenopausal women. *Hum Reprod* 2005a;**20**:1090–1099.

Chwalisz K, Perez MC, DeManno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. *Endocr Rev* 2005b;**26**:423–438.

Coutifaris C, Myers ER, Guzick DS, Diamond MP, Carson SA, Legro RS, McGovern PG, Schlaff WD, Carr BR, Steinkampf MP *et al*. Histological dating of timed endometrial biopsy tissue is not related to fertility status. *Fertil Steril* 2004;**82**:1264–1272.

Crissman JD, Azoury RS, Barnes AE, Schellhas HF. Endometrial carcinoma in women 40 years of age or younger. *Obstet Gynecol* 1981;**57**:699–704.

Critchley HO, Brenner RM, Henderson TA, Williams K, Nayak NR, Slayden OD, Millar MR, Saunders PT. Estrogen receptor beta, but not estrogen receptor alpha, is present in the vascular endothelium of the human and nonhuman primate endometrium. *J Clin Endocrinol Metab* 2001;**86**:1370–1378.

Critchley HO, Wang H, Jones RL, Kelly RW, Drudy TA, Gebbie AE, Buckley CH, McNeilly AS, Glasier AF. Morphological and functional features of endometrial decidualization following long-term intrauterine levonorgestrel delivery. *Hum Reprod* 1998a;**13**:1218–1224.

Critchley HO, Wang H, Kelly RW, Gebbie AE, Glasier AF. Progestin receptor isoforms and prostaglandin dehydrogenase in the endometrium of women using a levonorgestrel-releasing intrauterine system. *Hum Reprod* 1998b; **13**:1210–1217.

Critchley HO, Warner P, Lee AJ, Brechin S, Guise J, Graham B. Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status. *Health Technol Assess* 2004;**8**:iii–139.

Croxatto HB, Kovacs L, Massai R, Resch BA, Fuentealba B, Salvatierra AM, Croxatto HD, Zalanyi S, Viski S, Krenacs L. Effects of long-term low-dose mifepristone on reproductive function in women. *Hum Reprod* 1998a;**13**:793–798.

Croxatto HB, Massai MR, Salvatierra AM, Fuentealba B, Croxatto HD, Lahteenmaki P. Effects of a sequential regimen of mifepristone-medroxyprogesterone acetate on ovarian function, endometrial development and hormonal parameters. *Contraception* 1996;**54**:79–86.

Croxatto HB, Salvatierra AM, Croxatto HD, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. *Hum Reprod* 1993;**8**:201–207.

Croxatto HB, Salvatierra AM, Fuentealba B, Massai R. Contraceptive potential of a mifepristone-nomegestrol acetate sequential regimen in women. *Hum Reprod* 1998b;**13**:3297–3302.

de Kroon CD, de Bock GH, Dieben SW, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. *BJOG* 2003;**110**:938–947.

de Sa Rosa e Silva AC, Rosa e Silva JC, dos Reis FJ, Nogueira AA, Ferriani RA. Routine office hysteroscopy in the investigation of infertile couples before assisted reproduction. *J Reprod Med* 2005;**50**:501–506.

DeManno D, Elger W, Garg R, Lee R, Schneider B, Hess-Stumpp H, Schubert G, Chwalisz K. Asoprisnil (J867): a selective progesterone receptor modulator for gynecological therapy. *Steroids* 2003;**68**: 1019–1032.

DeWaay DJ, Syrop CH, Nygaard IE, Davis WA, Van Voorhis BJ. Natural history of uterine polyps and leiomyomata. *Obstet Gynecol* 2002;**100**: 3–7.

DeZiegler D, Fanchin R, Moustier de B, Bulletti C. The hormonal control of endometrial receptivity: estrogen (E2) and progesterone. *J Reprod Immunol* 1998;**39**:149–166.

Dueholm M, Forman A, Jensen ML, Laursen H, Kracht P. Transvaginal sonography combined with saline contrast sonohysterography in evaluating the uterine cavity in premenopausal patients with abnormal uterine bleeding. *Ultrasound Obstet Gynecol* 2001;**18**:54–61.

Dueholm M, Lundorf E, Olesen F. Imaging techniques for evaluation of the uterine cavity and endometrium in premenopausal patients before minimally invasive surgery. *Obstet Gynecol Surv* 2002;**57**:388–403.

Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. *J Minim Invasive Gynecol* 2005;**12**:227–233.

Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. *Obstet Gynecol* 2003;**101**: 243–250.

Elger W, Bartley J, Schneider B, Kaufmann G, Schubert G, Chwalisz K. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. *Steroids* 2000;**65**:713–723.

Escudero EL, Boerrigter PJ, Bennink HJ, Epifanio R, Horcajadas JA, Olivennes F, Pellicer A, Simon C. Mifepristone is an effective oral alternative for the prevention of premature luteinizing hormone surges and/or premature luteinization in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. *J Clin Endocrinol Metab* 2005;**90**:2081–2088.

Farquhar CM, Lethaby A, Sowter M, Verry J, Baranyai J. An evaluation of risk factors for endometrial hyperplasia in premenopausal women with abnormal menstrual bleeding. *Am J Obstet Gynecol* 1999;**181**:525–529.

Ferenczy A. Pathophysiology of endometrial bleeding. *Maturitas* 2003;**45**: 1–14.

Ferenczy A, Mutter G. Endometrial hyperplasia and neoplasia: definition, diagnosis and management principles. In: Sciarra JJ (ed). *Gynecology and Obstetrics Looseleaf CD-ROM*. Philadelphia: Lippincott Williams & WilkinsPhiladelphia, 2004.

Fernandez-Valdivia R, Mukherjee A, Mulac-Jericevic B, Conneely OM, DeMayo FJ, Amato P, Lydon JP. Revealing progesterone's role in uterine and mammary gland biology: insights from the mouse. *Semin Reprod Med* 2005;**23**:22–37.

Flores BH, Kenna H, Keller J, Solvason HB, Schatzberg AF. Clinical and biological effects of mifepristone treatment for psychotic depression. *Neuropsychopharmacology* 2006;**31**:628–636.

Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. *Obstet Gynecol* 1984;**64**:417–420.

Garry R, Khair A, Mooney P, Stuart M. A comparison of goserelin and danazol as endometrial thinning agents prior to endometrial laser ablation. *Br J Obstet Gynaecol* 1996;**103**:339–344.

Gemzell-Danielsson K, van Heusden AM, Killick SR, Croxatto HB, Bouchard P, Cameron S, Bygdeman M. Improving cycle control in progestogen-only contraceptive pill users by intermittent treatment with a new anti-progestogen. *Hum Reprod* 2002;**17**:2588–2593.

Gemzell-Danielsson K, Swahn ML, Svalander P, Bygdeman M. Early luteal phase treatment with mifepristone (RU 486) for fertility regulation. *Hum Reprod* 1993;**8**:870–873.

Gemzell-Danielsson K, Swahn ML, Westlund P, Johannisson E, Seppala M, Bygdeman M. Effect of low daily doses of mifepristone on ovarian function and endometrial development. *Hum Reprod* 1997;**12**: 124–131.

Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. *Int J Cancer* 1983;**31**:13–20.

Giudice LC. Genomics' role in understanding the pathogenesis of endometriosis. *Semin Reprod Med* 2003;**21**:119–124.

Godfrey EM, Mawson JT, Stanwood NL, Fielding SL, Schaff EA. Low-dose mifepristone for contraception: a weekly versus planned postcoital randomized pilot study. *Contraception* 2004;**70**:41–46.

Goldchmit R, Katz Z, Blickstein I, Caspi B, Dgani R. The accuracy of endometrial pipelle sampling with and without sonographic measurement of endometrial thickness. *Obstet Gynecol* 1993;**82**: 727–730.

Goldstein SR, Monteagudo A, Popiolek D, Mayberry P, Timor-Tritsch I. Evaluation of endometrial polyps. *Am J Obstet Gynecol* 2002;**186**: 669–674.

Gravanis A, Schaison G, George M, de Brux J, Satyaswaroop PG, Baulieu EE, Robel P. Endometrial and pituitary responses to the steroidal antiprogestin RU 486 in postmenopausal women. *J Clin Endocrinol Metab* 1985;**60**:156–163.

Gregory CW, Wilson EM, Apparao KB, Lininger RA, Meyer WR, Kowalik A, Fritz MA, Lessey BA. Steroid receptor coactivator expression throughout the menstrual cycle in normal and abnormal endometrium. *J Clin Endocrinol Metab* 2002;**87**:2960–2766.

Gronroos M, Salmi TA, Vuento MH, Jalava EA, Tyrkko JE, Maatela JI, Aromaa AR, Siegberg R, Savolainen ER, Kauraniemi TV. Mass screening for endometrial cancer directed in risk groups of patients with diabetes and patients with hypertension. *Cancer* 1993;**71**:1279–1282.

Grow DR, Iromloo K. Oral contraceptives maintain a very thin endometrium before operative hysteroscopy. *Fertil Steril* 2006;**85**:204–207.

Grunberg SM, Weiss MH, Russell CA, Spitz IM, Ahmadi J, Sadun A, Sitruk-Ware R. Long-term administration of mifepristone (RU486): clinical tolerance during extended treatment of meningioma. *Cancer Invest* 2006;**24**:727–733.

Hall JM, McDonnell DP. Coregulators in nuclear estrogen receptor action: from concept to therapeutic targeting. *Mol Interv* 2005;**5**:343–357.

Hecht JL, Ince TA, Baak JP, Baker HE, Ogden MW, Mutter GL. Prediction of endometrial carcinoma by subjective endometrial intraepithelial neoplasia diagnosis. *Mod Pathol* 2005;**18**:324–330.

Heidebrecht HJ, Buck F, Steinmann J, Sprenger R, Wacker HH, Parwaresch R. p100: a novel proliferation-associated nuclear protein specifically restricted to cell cycle phases S, G2, and M. *Blood* 1997;**90**:226–233.

Henderson TA, Saunders PT, Moffett-King A, Groome NP, Critchley HO. Steroid receptor expression in uterine natural killer cells. *J Clin Endocrinol Metab* 2003;**88**:440–449.

Herrmann W, Wyss R, Riondel A, Philibert D, Teutsch G, Sakiz E, Baulieu EE. The effects of an antiprogesterone steroid in women: interruption of the menstrual cycle and of early pregnancy. *C R Seances Acad Sci III* 1982; **294**:933–938.

Hinckley MD, Milki AA. 1000 office-based hysteroscopies prior to in vitro fertilization: feasibility and findings. *JSLS* 2004;**8**:103–107.

Ho SP, Tan KT, Pang MW, Ho TH. Endometrial hyperplasia and the risk of endometrial carcinoma. *Singapore Med J* 1997;**38**:11–15.

Hsu CL, Chen YL, Yeh S, Ting HJ, Hu YC, Lin H, Wang X, Chang C. The use of phage display technique for the isolation of androgen receptor interacting peptides with (F/W)XXL(F/W) and FXXLY new signature motifs. *J Biol Chem* 2003;**278**:23691–23698.

Hunter RW, Williams KE, Buck M, Hammond IG. Metastatic small cell carcinoma of the endometrium: prolonged remission and possible cure following chemotherapy. *Int J Gynecol Cancer* 1994;**4**:127–130.

Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivela A, Kujansuu E, Vuorma S, Yliskoski M, Paavonen J. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. *JAMA* 2004;**291**:1456–1463.

Imaoka I, Sugimura K, Masui T, Takehara Y, Ichijo K, Naito M. Abnormal uterine cavity: differential diagnosis with MR imaging. *Magn Reson Imaging* 1999;**17**:1445–1455.

Jain JK, Nicosia AF, Nucatola DL, Lu JJ, Kuo J, Felix JC. Mifepristone for the prevention of breakthrough bleeding in new starters of depo-medroxyprogesterone acetate. *Steroids* 2003;**68**:1115–1119.

Jeffrey JF, Krepart GV, Lotocki RJ. Papillary serous adenocarcinoma of the endometrium. *Obstet Gynecol* 1986;**67**:670–674.

Johannisson E, Landgren BM, Rohr HP, Diczfalusy E. Endometrial morphology and peripheral hormone levels in women with regular menstrual cycles. *Fertil Steril* 1987;**48**:401–408.

Kao LC, Germeyer A, Tulac S, Lobo S, Yang JP, Taylor RN, Osteen K, Lessey BA, Giudice LC. Expression profiling of endometrium from women with endometriosis reveals candidate genes for disease-based implantation failure and infertility. *Endocrinology* 2003;**144**:2870–2881.

Kettel LM, Murphy AA, Morales AJ, Ulmann A, Baulieu EE, Yen SS. Treatment of endometriosis with the antiprogesterone mifepristone (RU486). *Fertil Steril* 1996;**65**:23–28.

Koering MJ, Healy DL, Hodgen GD. Morphologic response of endometrium to a progesterone receptor antagonist, RU486, in monkeys. *Fertil Steril* 1986;**45**:280–287.

Kovacs P, Matyas S, Boda K, Kaali SG. The effect of endometrial thickness on IVF/ICSI outcome. *Hum Reprod* 2003;**18**:2337–2341.

Krikun G, Critchley H, Schatz F, Wan L, Caze R, Baergen RN, Lockwood CJ. Abnormal uterine bleeding during progestin-only contraception may result from free radical-induced alterations in angiopoietin expression. *Am J Pathol* 2002;**161**:979–986.

Krikun G, Schatz F, Taylor R, Critchley HO, Rogers PA, Huang J, Lockwood CJ. Endometrial endothelial cell steroid receptor expression and steroid effects on gene expression. *J Clin Endocrinol Metab* 2005;**90**:1812–1818.

Kurman RJ, Felix JC, Archer DF, Nanavati N, Arce J, Moyer DL. Norethindrone acetate and estradiol-induced endometrial hyperplasia. *Obstet Gynecol* 2000;**96**:373–379.

Kurman RJ, Kaminski PF, Norris HJ. The behavior of endometrial hyperplasia. A long-term study of 'untreated' hyperplasia in 170 patients. *Cancer* 1985;**56**:403–412.

Lahteenmaki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, Nilsson CG. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *BMJ* 1998; **316**:1122–1126.

Lebovic DI, Shifren JL, Ryan IP, Mueller MD, Korn AP, Darney PD, Taylor RN. Ovarian steroid and cytokine modulation of human endometrial angiogenesis. *Hum Reprod* 2000;**15**(Suppl. 3):67–77.

Ledger WL, Sweeting VM, Hillier H, Baird DT. Inhibition of ovulation by low-dose mifepristone (RU 486). *Hum Reprod* 1992;**7**:945–950.

Leslie KK, Kumar NS, Richer J, Owen G, Takimoto G, Horwitz KB, Lange C. Differential expression of the A and B isoforms of progesterone receptor in human endometrial cancer cells. Only progesterone receptor B is induced by estrogen and associated with strong transcriptional activation. *Ann N Y Acad Sci* 1997;**828**:17–26.

Lessey BA. Two pathways of progesterone action in the human endometrium: implications for implantation and contraception. *Steroids* 2003;**68**: 809–815.

Lessey BA, Castelbaum AJ, Wolf L, Greene W, Paulson M, Meyer WR, Fritz MA. Use of integrins to date the endometrium. *Fertil Steril* 2000;**73**: 779–787.

Machtinger R, Korach J, Padoa A, Fridman E, Zolti M, Segal J, Yefet Y, Goldenberg M, Ben-Baruch G. Transvaginal ultrasound and diagnostic hysteroscopy as a predictor of endometrial polyps: risk factors for premalignancy and malignancy. *Int J Gynecol Cancer* 2005;**15**:325–328.

Marions L, Danielsson KG, Swahn ML, Bygdeman M. Contraceptive efficacy of low doses of mifepristone. *Fertil Steril* 1998;**70**:813–816.

Marions L, Viski S, Danielsson KG, Resch BA, Swahn ML, Bygdeman M, Kovacs L. Contraceptive efficacy of daily administration of 0.5 mg mifepristone. *Hum Reprod* 1999;**14**:2788–2790.

Martineau PA, Levental M. Large endometrial polyp in a patient on long-term mifepristone therapy. *J Ultrasound Med* 2000;**19**:487–489.

Massai MR, Pavez M, Fuentealba B, Croxatto HB, d'Arcangues C. Effect of intermittent treatment with mifepristone on bleeding patterns in Norplant implant users. *Contraception* 2004;**70**:47–54.

McClellan M, West NB, Brenner RM. Immunocytochemical localization of estrogen receptors in the macaque endometrium during the luteal-follicular transition. *Endocrinology* 1986;**119**:2467–2475.

McDonnell DP, Chang CY, Norris JD. Development of peptide antagonists that target estrogen receptor-cofactor interactions. *J Steroid Biochem Mol Biol* 2000;**74**:327–335.

McGEE WB. Carcinoma of the endometrium in women under forty years of age; report of three cases. *Obstet Gynecol* 1958;**11**:388–390.

McGowan EM, Saad S, Bendall LJ, Bradstock KF, Clarke CL. Effect of progesterone receptor a predominance on breast cancer cell migration into bone marrow fibroblasts. *Breast Cancer Res Treat* 2004;**83**:211–220.

Mirkin S, Archer DF. Effects of mifepristone on vascular endothelial growth factor and thrombospondin-1 mRNA in Ishikawa cells: implication for the endometrial effects of mifepristone. *Contraception* 2004;**70**: 327–333.

Mote PA, Bartow S, Tran N, Clarke CL. Loss of co-ordinate expression of progesterone receptors A and B is an early event in breast carcinogenesis. *Breast Cancer Res Treat* 2002;**72**:163–172.

Mote PA, Leary JA, Avery KA, Sandelin K, Chenevix-Trench G, Kirk JA, Clarke CL, kConFab Investigators. Germ-line mutations in BRCA1 or BRCA2 in the normal breast are associated with altered expression of estrogen-responsive proteins and the predominance of progesterone receptor A. *Genes Chromosomes Cancer* 2004;**39**:236–248.

Murphy AA, Kettel LM, Morales AJ, Roberts V, Parmley T, Yen SS. Endometrial effects of long-term low-dose administration of RU486. *Fertil Steril* 1995;**63**:761–766.

Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SS. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. *J Clin Endocrinol Metab* 1993;**76**:513–517.

Mutter GL, Baak JP, Crum CP, Richart RM, Ferenczy A, Faquin WC. Endometrial precancer diagnosis by histopathology, clonal analysis, and computerized morphometry. *J Pathol* 2000a;**190**:462–469.

Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. *Cancer Res* 2001;**61**:4311–4314.

Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Eng C. Changes in endometrial PTEN expression throughout the human menstrual cycle. *J Clin Endocrinol Metab* 2000b;**85**:2334–2338.

Myers ER, Silva S, Barnhart K, Groben PA, Richardson MS, Robboy SJ, Leppert P, Coutifaris C. Interobserver and intraobserver variability in the histological dating of the endometrium in fertile and infertile women. *Fertil Steril* 2004;**82**:1278–1282.

Narvekar N, Cameron S, Critchley HO, Lin S, Cheng L, Baird DT. Low–dose mifepristone inhibits endometrial proliferation and up-regulates androgen receptor. *J Clin Endocrinol Metab* 2004;**89**:2491–2497.

Narvekar N, Critchley HO, Cheng L, Baird DT. Mifepristone-induced amenorrhoea is associated with an increase in microvessel density and glucocorticoid receptor and a decrease in stromal vascular endothelial growth factor. *Hum Reprod* 2006;**21**:2312–2318.

Newfield RS, Spitz IM, Isacson C, New MI. Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. *Clin Endocrinol (Oxf)* 2001;**54**:399–404.

Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW, Loriaux DL. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J Clin Endocrinol Metab* 1985;**61**:536–540.

Nisker JA, Ramzy I, Collins JA. Adenocarcinoma of the endometrium and abnormal ovarian function in young women. *Am J Obstet Gynecol* 1978;**130**:546–550.

Novac L, Grigore T, Cernea N, Niculescu M, Cotarcea S. Incidence of endometrial carcinoma in patients with endometrial hyperplasia. *Eur J Gynaecol Oncol* 2005;**26**:561–563.

Noyes RW. Uniformity of secretory endometrium. *Obstet Gynecol* 1956;**7**: 221–228.

Noyes RW. Endometrial development and fertility. *J Miss State Med Assoc* 1963;**4**:5–7.

Paulson RJ, Sauer MV, Lobo RA. Potential enhancement of endometrial receptivity in cycles using controlled ovarian hyperstimulation with antiprogestins: a hypothesis. *Fertil Steril* 1997;**67**:321–325.

PEPI Trial Writing Group. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The PEPI trial. *JAMA* 1996;**275**:370–375.

Perrault D, Eisenhauer EA, Pritchard KI, Panasci L, Norris B, Vandenberg T, Fisher B. Phase II study of the progesterone antagonist mifepristone in patients with untreated metastatic breast carcinoma: a National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol* 1996;**14**:2709–2712.

Peterson EP. Endometrial carcinoma in young women. A clinical profile. *Obstet Gynecol* 1968;**31**:702–707.

Pomara N, Doraiswamy PM, Tun H, Ferris S. Mifepristone (RU 486) for Alzheimer's disease. *Neurology* 2002;**58**:1436.

Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. *Cancer Res* 1997;**57**:4736–4738.

Rocereto TF, Saul HM, Aikins JA Jr, Paulson J. Phase II study of mifepristone (RU486) in refractory ovarian cancer. *Gynecol Oncol.* 2000;**77**:429–432.

Ronkin S, Northington R, Baracat E, Nunes MG, Archer DF, Constantine G, Pickar JH. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. *Obstet Gynecol* 2005;**105**:1397–1404.

Salamonsen LA, Kovacs GT, Findlay JK. Current concepts of the mechanisms of menstruation. *Baillieres Best Pract Res Clin Obstet Gynaecol* 1999;**13**:161–179.

Sampath D, Winneker RC, Zhang Z. The angiogenic factor Cyr61 is induced by the progestin R5020 and is necessary for mammary adenocarcinoma cell growth. *Endocrine* 2002;**18**:147–159.

Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, Bovicelli L. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. *Am J Obstet Gynecol* 2003;**188**:927–931.

Savoldi G, Ferrari F, Ruggeri G, Sobek L, Albertini A, Di LD. Progesterone agonists and antagonists induce down- and up-regulation of estrogen receptors and estrogen inducible genes in human breast cancer cell lines. *Int J Biol Markers* 1995;**10**:47–54.

Schubert G, Elger W, Kaufmann G, Schneider B, Reddersen G, Chwalisz K. Discovery, chemistry, and reproductive pharmacology of asoprisnil and related 11beta-benzaldoxime substituted selective progesterone receptor modulators (SPRMs). *Semin Reprod Med* 2005;**23**:58–73.

Scully RE, Bonfiglio TA, Kurman RJ, Silverberg SG, Wilkinson DS. *Histological Typing of Female Genital Tract Tumours*, 2nd edn. New York: Springer-Verlag, New York, 1994.

Shokeir TA, Shalan HM, El, Shafei MM. Significance of endometrial polyps detected hysteroscopically in eumenorrheic infertile women. *J Obstet Gynaecol Res* 2004;**30**:84–89.

Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? *Gynecol Obstet Invest* 2004;**58**:212–215.

Shutter J, Wright TC Jr. Prevalence of underlying adenocarcinoma in women with atypical endometrial hyperplasia. *Int J Gynecol Pathol* 2005;**24**: 313–318.

Simpson GM, El Sheshai A, Loza N, Kingsbury SJ, Fayek M, Rady A, Fawzy W. An 8-week open-label trial of a 6-day course of mifepristone for the treatment of psychotic depression. *J Clin Psychiatry* 2005;**66**:598–602.

Smid-Koopman E, Kuhne LC, Hanekamp EE, Gielen SC, De Ruiter PE, Grootegoed JA, Helmerhorst TJ, Burger CW, Brinkmann AO, Huikeshoven FJ *et al*. Progesterone-induced inhibition of growth and differential regulation of gene expression in PRA- and/or PRB-expressing endometrial cancer cell lines. *J Soc Gynecol Investig* 2005;**12**:285–292.

Smith CL, O'Malley BW. Coregulator function: a key to understanding tissue specificity of selective receptor modulators. *Endocr Rev* 2004; **25**:45–71.

Spitz IM, Grunberg SM, Chabbert-Buffet N, Lindenberg T, Gelber H, Sitruk-Ware R. Management of patients receiving long-term treatment with mifepristone. *Fertil Steril* 2005;**84**:1719–1726.

Steinauer J, Pritts EA, Jackson R, Jacoby AF. Systematic review of mifepristone for the treatment of uterine leiomyomata. *Obstet Gynecol* 2004;**103**:1331–1336.

Swahn ML, Bygdeman M, Cekan S, Xing S, Masironi B, Johannisson E. The effect of RU 486 administered during the early luteal phase on bleeding pattern, hormonal parameters and endometrium. *Hum Reprod* 1990; **5**:402–408.

Talbi S, Hamilton AE, Vo KC, Tulac S, Overgaard MT, Dosiou C, Le Shay N, Nezhat CN, Kempson R, Lessey BA *et al*. Molecular phenotyping of human endometrium distinguishes menstrual cycle phases and underlying biological processes in normo-ovulatory women. *Endocrinology* 2006;**147**:1097–1121.

Valenzuela P, Sanz JM, Keller J. Atypical endometrial hyperplasia: grounds for possible misdiagnosis of endometrial adenocarcinoma. *Gynecol Obstet Invest* 2003;**56**:163–167.

Voipio SK, Komi J, Kangas L, Halonen K, DeGregorio MW, Erkkola RU. Effects of ospemifene (FC-1271a) on uterine endometrium, vaginal maturation index, and hormonal status in healthy postmenopausal women. *Maturitas* 2002;**43**:207–214.

von Hertzen H, Van Look PF. Antiprogestins for contraception? *Semin Reprod Med* 2005;**23**:92–100.

Walker MJ, Chaudhuri PK, Beattie CW, Das Gupta TK. Steroid receptors in malignant skeletal tumors. *Cancer* 1980;**45**:3004–3007.

Walsh JW. Computed tomography of gynecologic neoplasms. *Radiol Clin North Am* 1992;**30**:817–830.

Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen LA, Findlay JK, Fraser IS. A pilot study to assess the effect of three short-term treatments on frequent and/or prolonged bleeding compared to placebo in women using Implanon. *Hum Reprod* 2006;**21**:295–302.

Westendorf JM, Rao PN, Gerace L. Cloning of cDNAs for M-phase phosphoproteins recognized by the MPM2 monoclonal antibody and determination of the phosphorylated epitope. *Proc Natl Acad Sci USA* 1994;**91**:714–718.

Widra EA, Dunton CJ, McHugh M, Palazzo JP. Endometrial hyperplasia and the risk of carcinoma. *Int J Gynecol Cancer* 1995;**5**:233–235.

Wilcox AJ, Baird DD, Weinberg CR. Time of implantation of the conceptus and loss of pregnancy. *N Engl J Med* 1999;**340**:1796–1799.

Winkler B, Alvarez S, Richart RM, Crum CP. Pitfalls in the diagnosis of endometrial neoplasia. *Obstet Gynecol* 1984;**64**:185–194.

Wolkowitz OM, Reus VI. Treatment of depression with antiglucocorticoid drugs. *Psychosom Med* 1999;**61**:698–711.

Wright TC, Holinka CF, Ferenczy A, Gatsonis CA, Mutter GL, Nicosia S, Richart RM. Estradiol-induced hyperplasia in endometrial biopsies from women on hormone replacement therapy. *Am J Surg Pathol* 2002;**26**:1269–1275.

Young AH, Gallagher P, Watson S, Del Estal D, Owen BM, Ferrier IN. I. Improvements in neurocognitive function and mood following adjunctive treatment with mifepristone (RU-486) in bipolar disorder. *Neuropsychopharmacology* 2004;**29**:1538–1545.

Zaino RJ. Endometrial hyperplasia: is it time for a quantum leap to a new classification? *Int J Gynecol Pathol* 2000;**19**:314–321.

Zeng C, Gu M, Huang H. A clinical control study on the treatment of uterine leiomyoma with gonadotrophin releasing hormone agonist or mifepristone. *Zhonghua Fu Chan Ke Za Zhi* 1998;**33**:490–492.

Submitted on March 22, 07; resubmitted on May 14, 2007; accepted on June 6, 2007