GENERAL GYNECOLOGY

Intrauterine progestins, progesterone antagonists, and receptor modulators: a review of gynecologic applications

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Intrauterine progestins, progesterone receptor modulators, and antagonists have many important current and potential gynecologic applications. This article will describe the evidence for use of intrauterine progestin for common gynecologic conditions beyond its important role in contraception. We will review the evidence for use of intrauterine progestin delivery for menorrhagia, endometriosis management, adenomyosis treatment, uterine fibroids, endometrial hyperplasia, and its concurrent use in women on hormone replacement therapy or tamoxifen.

Key words: intrauterine progestin, leiomyomas, levonorgestrel intrauterine device, menorrhagia, progesterone receptor modulators

Progesterone is a key hormone in regulating the female reproductive system, interacting at the level of the hypothalamus, ovary, uterus, and breast. Progesterone exerts effects on ovulation, endometrial differentiation, cervical mucus, breast differentiation, and uterine contractility.[1,2] Given their wide range of activity, progestins and their analogs and antagonists have many uses in gynecology, including contraception, emergency contraception, management of miscarriage, medical abortion, and treatment of conditions related to endometrial and myometrial growth.

Progestins are available for oral, injectable, implantable, and intrauterine delivery.[2] Intrauterine delivery of progestin is an effective way to administer local treatment and bypass systemic side effects. Intrauterine drug delivery is underutilized in the United States, perhaps because of myths that limit its use.[3] For example, only 1.3% of US women use an intrauterine device for contraception, as compared with 15–23% of women in European countries and 18–28% of American, female gynecologists.[3-5]

In addition to providing highly effective contraception, intrauterine progestin delivery is safe and effective in the management of menorrhagia, dysmenorrhea, uterine myomata, and endometrial proliferation.[6] Research into novel progesterone receptor modulators and antagonists is an active area of study.[7]

This article will describe the evidence for use of intrauterine progestins and receptor modulators for common gynecologic conditions in addition to their important role in contraception. We will review the evidence for use of intrauterine progestin delivery for menorrhagia, endometriosis management, adenomyosis, uterine fibroids, endometrial hyperplasia, and its concurrent use in women on hormone replacement therapy or tamoxifen.

Methods

We searched PubMed and the Cochrane databases from inception through May 15, 2009, using a combination of key words and text words related to intrauterine progestin, selective progesterone receptor modulators, progesterone antagonists, levonorgestrel intrauterine devices, menorrhagia, adenomyosis, leiomyomas, endometrial hyperplasia, endometriosis management, and tamoxifen. No language restrictions were applied, and references were reviewed for additional relevant publications. Preference was given to randomized, controlled trials and articles published within the last 10 years.

Pharmacology

Many different progestins are used in oral and implantable contraceptives; however, only 1 form of intrauterine delivery is currently approved for use in the United States. The levonorgestrel intrauterine system (LNG IUS, Mirena; Bayer HealthCare Pharmaceuticals, Wayne, NJ) is a T-shaped device, with a reservoir containing 52 mg of levonorgestrel. In vivo, the hormone is released at an initial rate of 20 μg daily, which progressively declines to half of this rate by 5 years.[2] Levonorgestrel is a 19-nortestosterone derivative and exhibits a profound progestational effect on the endometrium.[8] The endometrial lining becomes atrophic and inactive and cervical mucus becomes thick and scant.[2] The majority of cycles are ovulatory.[2]

Progesterone antagonists and selective progesterone receptor modulators

In addition to the potential for the LNG IUS to be approved for other uses, progesterone antagonists (PAs) and selective progesterone receptor modulators (SPRMs) hold the promise of many valuable applications in gynecology. Progesterone exerts its effects on target tissues by means of ligand-activated progesterone receptors. When the receptor is activated, it regulates the transcription of

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key genes.[9] PAs and SPRMSs modify this process.

Pure progesterone antagonists have antiproliferative effects on the endometrium, suppress late follicular development, and block the midcycle surge of luteinizing hormone.[7] These characteristics suggest the potential for contraceptive use.[7] Mifepristone is the best-known PA and competes for binding of the progesterone receptor with an inactive ligand.[9] Mifepristone is currently approved for use in medication abortion, and 3 small trials have demonstrated a reduction in endometriosis symptoms with mifepristone therapy.[2,7]

SPRMs are a class of compounds with mixed antagonist and agonist effects on the progesterone receptor. Whether these compounds act as an agonist or antagonist depends on the cellular and tissue context.[10] Coregulators are present in varying levels in different types of cells and tissues.[11] Their presence modulates the ability of the progesterone receptor to transcribe deoxyribonucleic acid. Coregulators can amplify the transcription process or halt it completely.[11] Currently the subject of intensive study, SPRMs such as VA 2914, CDB2914, and J867 (Asoprisnil; Bayer Schering Pharma, Berlin, Germany) may ultimately play an important role in management of fibroids, endometriosis, and fertility control.[1,7]

Menorrhagia

Menorrhagia is excessive blood loss with menstruation (>80 mL blood loss or menses lasting >7 days' duration) and is a common gynecologic complaint.[12] The prevalence of menorrhagia increases through the perimenopausal period. Menstrual disorders affect 10–15% of women and are a common indication for hysterectomy in the United States.[12,13] One-third of women in the United States undergo a hysterectomy, a rate much higher than in Western Europe.[13] This difference may be due in part to lower utilization of the LNG IUS to control menorrhagia in the United States. Hysterectomy is a major surgery and entails greater risks and costs than medical treatment. Whereas hysterectomy remains a viable option for menorrhagia refractory to medical management, the LNG IUS is underutilized to control menorrhagia.[14]

The LNG IUS has been evaluated for its impact on menstrual blood loss and acceptability as an alternative to hysterectomy.[12,14-18] Menstrual blood loss with the LNG IUS was reduced by 86% at 3 months and 97% at 6 months, and parameters of anemia, such as hematocrit and ferritin levels, improved.[15] The improvement in menorrhagia noted with the LNG IUS is superior to that reported from use of oral contraceptives, tranexaminic acid, and prostaglandin synthetase inhibitors, which are all used in the medical management of excessive bleeding.[13]

Endometrial ablation is a commonly used procedure in the surgical management of menorrhagia.[19] A range of techniques and devices are available for endometrial ablation. The thermal balloon is a popular global ablation device that allows transcervical destruction of the endometrium.[19] The LNG IUS has been compared with thermal balloon ablation and manual hysteroscopic ablation for reduction of blood loss, patient satisfaction, and cost.[19-21] At 12 and 24 months of follow-up, women treated with the LNG IUS had significantly higher rates of amenorrhea than those in the ablation group ($P = .025$).

A recent metaanalysis of 6 randomized controlled trials comparing the LNG IUS with endometrial ablation showed that outcomes, including quality of life measures, were comparable between the 2 methods at 2 years of follow-up.[22] Cost-effectiveness analysis also supports the LNG IUS as preferable in terms of direct and indirect costs to thermal balloon ablation.[20]

An open, randomized study compared the acceptability of the LNG IUS with hysterectomy for women with menorrhagia. Women in Finland scheduled to undergo hysterectomy for menorrhagia and awaiting surgery were randomized to either LNG IUS insertion or to continue their current medical management.[23] The primary outcome was the proportion of women canceling hysterectomy at 6 months. At 6 months, 64% of women in the LNG IUS group had decided against hysterectomy, as compared with 14% of the control group ($P < .001$).[23] Five years of follow-up of women randomized to LNG IUS or hysterectomy showed equal satisfaction with treatment outcomes in both groups but lower costs in the LNG IUS group.[24]

One highly specific PA, ZK230211, has been compared with LNG IUS in terms of bleeding outcomes and endometrial morphology in 42 women scheduled to undergo hysterectomy.[25] In this randomized, blinded pilot study, intrauterine delivery of ZK230211 or levonorgestrel was administered 4–8 weeks prior to a woman's scheduled hysterectomy. Women receiving the LNG IUS had significantly increased number of days of bleeding, whereas those receiving ZK230211 did not.[25]

Irregular bleeding is a common complaint of women using progestin-only methods; this study suggests that intrauterine delivery of PA may improve on this side effect and also yield similar results. Clearly, further research in this area is needed (Table 1).

Endometriosis

Endometriosis, the presence of endometrial cells outside the uterus, is a common disorder of reproductive-age women.[26] Afflicting 7–20% of women, its harmful sequelae include infertility and chronic pelvic pain.[8,26] Among patients with chronic pelvic pain, 70–90% have endometriosis.[8] Therapy for endometriosis consists of surgical ablation of implants and medical treatments, including nonsteroidal antiinflammatory drugs, progestins such as depot medroxyprogesterone acetate, continuous oral contraceptives, gonadotropin-releasing hormone analogs (GnRHa) to induce a pseudomenopause, and androgen derivatives.[8] These medications have systemic side effects, such as estrogen deprivation, which limit the duration of their use.

The role of the LNG IUS in management of this common and troublesome disorder has been evaluated by multiple studies.[8,27-29] A pilot study examined the role of LNG IUS as a postoperative adjunct to surgical ablation for endometriosis.[30] When compared with expectant