3 cases of hormone therapy optimized to match the patient problem

There are 5 different dose combinations of ethinyl estradiol and norethindrone acetate, ranging from 2.5 µg to 30 µg of ethinyl estradiol, and a 6th option is norethindrone acetate monotherapy

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There are dozens of medications containing combinations of estrogen and progestin. I am often confused by the bewildering proliferation of generic brand names used to describe the same estrogen-progestin (E-P) regimen. For example, the combination medication containing ethinyl estradiol 20 µg plus norethindrone acetate (NEA) 1 mg is available under at least 5 different names: Lo Estrin 1/20 (Warner Chilcot), Junel 1/20 (Teva Pharmaceuticals), Microgestin Fe 1/20 (Mayne Pharma), Gildess 1/20 (Qualitest Pharmaceuticals), and Larin 1/20 (Novast Laboratories). To reduce the confusion, it is often useful to select a single preferred estrogen and progestin and use the dose combinations that are available to treat a wide range of gynecology problems (**TABLE**, page 13). In this editorial I focus on using various dose combinations of ethinyl estradiol and NEA to treat 3 common gynecologic problems.

CASE 1 Polycystic ovary syndrome

A 19-year-old woman reports 4 spontaneous menses in the past year and bothersome facial hair and acne. Her total testosterone concentration is at the upper limit of normal (0.46 ng/mL) and her sex hormone binding globulin (SHBG) concentration is at the lower limit of normal (35 nM). For treatment of the patient's menstrual disorder, what is an optimal E-P combination?

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Prioritize the use of an estrogen-dominant medication

Based on the Rotterdam criteria this woman has polycystic ovary syndrome (PCOS).[1] In women with PCOS, luteinizing hormone (LH) secretion is increased, stimulating excessive ovarian production of testosterone.[2] In addition, many women with PCOS have decreased hepatic secretion of SHBG, a binding protein that prevents testosterone from entering cells, resulting in excessive bioavailable testosterone.[3] The Endocrine Society recommends that women with PCOS who have menstrual dysfunction or hirsutism be treated initially with a combination E-P hormone medication.[1] Combination E-P medications suppress pituitary secretion of LH, thereby reducing ovarian production of testosterone, and ethinyl estradiol increases hepatic secretion of SHBG, reducing bioavailable testosterone. **These two goals are best accomplished with an oral E-P hormone medication containing ethinyl estradiol doses of 20 µg to 30 µg per pill.** An E-P hormone medication containing pills with an ethinyl estradiol dose ≤ 10 µg daily may stimulate less hepatic production of SHBG than a pill with an ethinyl estradiol dose of 20 µg or 30 µg daily.[4,5] In addition, E-P pills containing levonorgestrel suppress SHBG hormone secretion compared with E-P pills with other progestins.[6] Therefore, levonorgestrel-containing E-P pills should not be prioritized for use in women with PCOS because the estrogen-induced increase in SHBG will be blunted by levonorgestrel.

CASE 2 Moderate to severe pelvic pain caused by endometriosis

A 25-year-old woman (G0) with severe dysmenorrhea had a laparoscopy showing endometriosis lesions in the cul-de-sac and a peritoneal window

CONTINUED ON PAGE 13

CONTINUED FROM PAGE 9

TABLE Estrogen-progestin pills with a wide dose range of ethinyl estradiol[a]

Brand name	Examples of generic brand names	Ethinyl estradiol dosage	Norethindrone acetate (NEA) dosage
Aygestin (Duramed Pharmaceuticals)	Norethindrone Acetate	0	5 mg NEA
FemHRT (Allergan)	Jevantique Lo	2.5 µg	0.5 mg NEA
FemHRT	Jinteli (Teva Pharmaceuticals), Jevantique (Watson Pharma)	5.0 µg	1.0 mg NEA
Lo LoEstrin Fe (Allergan)	No generic available	10 µg	1.0 mg NEA
Lo Estrin 1/20 (Warner Chilcot)	Junel Fe 1/20 (Teva Pharmaceuticals)	20 µg	1.0 mg NEA
Lo Estrin 1.5/30 (Warner Chilcot)	Junel 1.5/30 (Teva Pharmaceuticals)	30 µg	1.5 mg NEA

[a]Pills containing ethinyl estradiol ≤ 5 µg per pill are progestin dominant.

near the left uterosacral ligament. Biopsy showed endometriosis. Postoperatively, the patient was treated with an E-P pill containing 30 µg ethinyl estradiol and 0.15 mg desogestrel per pill using a continuous-dosing protocol. During the year following the laparoscopy, her pelvic pain symptoms gradually increased until they became severe, preventing her from performing daily activities on multiple days per month. She was prescribed elagolix but her insurance did not approve the treatment. What alternative treatment would you prescribe?

Use progestin-dominant pills to treat pelvic pain

Cellular activity in endometriosis lesions is stimulated by estradiol and inhibited by a high concentration of androgenic progestins or androgens. This simplified endocrine paradigm explains the effectiveness of hormonal treatments that suppress ovarian estradiol production, including leuprolide, elagolix, medroxyprogesterone acetate, and NEA. For the woman in the above case, I would advocate for elagolix treatment but, following the insurance denial of the prescription, **an alternative treatment for moderate or severe pelvic pain caused by endometriosis would be a progestin-dominant hormone medication (for example, NEA 5 mg daily).** Norethindrone acetate 5 mg daily may be associated with bothersome adverse effects including weight gain (16% of patients; mean weight gain, 3.1 kg), acne (10%), mood lability (9%), hot flashes (8%), depression (6%), scalp hair loss (4%), headache (4%), nausea (3%), and deepening of the voice (1%).[7]

I sometimes see women with moderate to severe pelvic pain caused by endometriosis being treated with norethindrone 0.35 mg daily. This dose of norethindrone is suboptimal for pain treatment because it does not reliably suppress ovarian production of estradiol. In addition, the cells in endometriosis lesions are often resistant to the effects of progesterone, requiring higher dosages to produce secretory or decidual changes. In most situations, I recommend against the use of norethindrone 0.35 mg daily for the treatment of pelvic pain caused by endometriosis.

Patients commonly ask if NEA 5 mg daily has contraceptive efficacy. Although it is not approved at this dosage by the US Food and Drug Administration as a contraceptive,[8] norethindrone 0.35 mg daily is approved as a progestin-only contraceptive.[9] Norethindrone acetate is rapidly and completely deacetylated to norethindrone and the disposition of oral NEA is indistinguishable from that of norethindrone (which is the FDA-approved dosage mentioned above). Since norethindrone 0.35 mg daily is approved as a contraceptive, it is highly likely that NEA 5 mg daily has contraceptive efficacy, especially if there is good adherence with the daily medication.

CASE 3 Perimenopausal AUB

A 45-year-old woman reports varying menstrual cycle lengths from 24 to 60 days with very heavy menses in some cycles. Pelvic ultrasonography shows no abnormality. Endometrial biopsy shows a proliferative endometrium. Her serum progesterone level, obtained 1 week before the onset of menses, is < 3 ng/mL. She has no past history of heavy menses, easy bruising, excessive bleeding with procedures, or a family history of bleeding problems. She also reports occasional hot flashes that wake her from sleep.

Use an estrogen step-down regimen to manage postmenopause transition

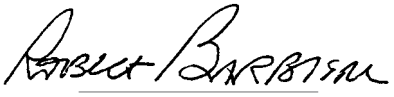
This patient is likely in the perimenopause transition, and the abnormal uterine bleeding (AUB) is caused, in part, by oligo- or anovulation. Perimenopausal women with AUB may have cycles characterized by above normal ovarian estradiol production and below normal progesterone

production, or frank anovulation.[10] Elevated ovarian estrogen and low progesterone production sets the stage for heavy bleeding in the perimenopause, regardless of the presence of uterine pathology such as fibroids.

For perimenopausal women, one option for treatment of AUB due to anovulation is to prescribe an estrogen step-down regimen. For the 45-year-old woman in this case, initiating treatment with an E-P pill containing ethinyl estradiol 10 µg and NEA 1 mg will likely control the AUB and her occasional hot flash.[11] As the woman ages, the ethinyl estradiol dose can be decreased to pills containing 5 µg and then 2.5 µg, covering the transition into postmenopause. Once the woman is in the postmenopause, treatment with transdermal estradiol and oral micronized progesterone is an option to treat menopausal vasomotor symptoms.

Optimize estrogen and progestin treatment for your patients

Many gynecologic problems are effectively treated by estrogen and/or progestin steroids. The dose of estrogen and progestin should be tailored to the specific problem. For PCOS, the estrogen dose selected should be sufficient to safely stimulate hepatic SHBG production. For endometriosis, if a GnRH antagonist is not available to the patient, a high-dose progestin, such as NEA 5 mg, may be an effective treatment. During the perimenopause transition in a woman with AUB, a treatment plan using a sequential E-P step-down program might control symptoms and help smoothly glide the patient into the postmenopause. ●



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