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Uses of Progesterone

Throughout a Woman's Life

Introduction:

An overview of progesterone and progestins

James A. Simon, MD

Secondary amenorrhea:

Uses of progesterone for induction of bleeding

James A. Simon, MD

Progesterone:

Uses in ART and prevention of pregnancy loss

Marcelle I. Cedars, MD

Progesterone and progestins in postmenopausal hormone therapy

Robert D. Langer, MD, MPH



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Target Audience

This activity has been designed to meet the educational needs of health professionals who care for women from adolescence to postmenopause.

Educational Objectives

At the conclusion of the educational activity, participants should be able to:

- Discuss the clinical potential and implications that progestins or progesterone have on the endometrium
- Distinguish differences among synthetic progestins and progesterone, with varying side-effect profiles and methods of administration
- Explain to patients how benefits and risks may affect them individually, based on their unique profile, before drawing conclusions or recommending hormone therapy

Accreditation Statement

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Introduction: An overview of progesterone and progestins

James A. Simon, MD

Progesterone, a hormone secreted by the ovaries, placenta, and adrenal glands, plays important roles in a woman's normal reproductive cycle. Its antiproliferative endometrial effects promote shedding of the endometrium and establish a regular menstrual cycle. During the luteal phase, progesterone is essential to maintain pregnancy.

Exogenous progestogen administration often is used to treat secondary amenorrhea, manage luteal phase deficiency, prevent endometrial hyperplasia, ameliorate dysfunctional uterine bleeding, and treat endometriosis. For a woman who has a uterus and who experiences menopausal symptoms, progesterone opposes estrogen's effects on the endometrium (e.g., progesterone reduces mitotic activity and exerts antiproliferative effects). Progestogens also are used in assisted reproductive technologies and in contraceptive agents and emergency contraceptive regimens.

This monograph will describe the uses of progesterone and progestins in several key areas across a woman's reproductive life. I will discuss its use in the treatment of secondary amenorrhea.

Dr Cedars will review the use of progesterone and other agents to provide luteal support for maintenance of a pregnancy and in assisted reproductive technologies.

Dr Langer will present recent updates from the Women's Health Initiative and other pivotal trials exploring the potential effects of progesterone and progestins in menopausal hormone therapy.

Differences among progestogens

As clinicians, we often fail to appreciate the differences among the exogenous progestogens. However, exogenous substances include both natural progesterone and synthetic and semi-synthetic progestins (FIGURE 1). These agents are structurally related—but are not identical—to either progesterone or testosterone. The synthetic progestins are those of the 19-norprogesterone group, the 17 α -hydroxyprogesterone derivatives, and the 19-nortestosterone group. The latter category of agents is divided further into 2 classes: the estranes and the gonanes.

While we often view these compounds as bioequivalent agents, progesterone and progestins differ not only in their structure, but also in their potency, as determined by standard bioassays. Further, investigations using animal models have evaluated the ability of progestins to transform the endometrium, as assessed by the McPhail Index, and to inhibit ovulation.¹ FIGURE 2 illustrates the order of potency, from left to right. It should be kept in mind that clinical trials featuring head-to-head comparisons of agents may or may not take differ-

FIGURE 1

Classification of exogenous progestogens

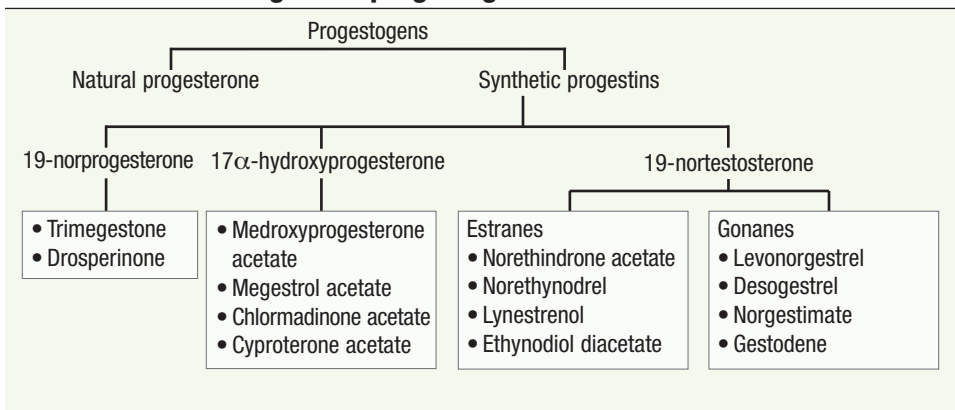
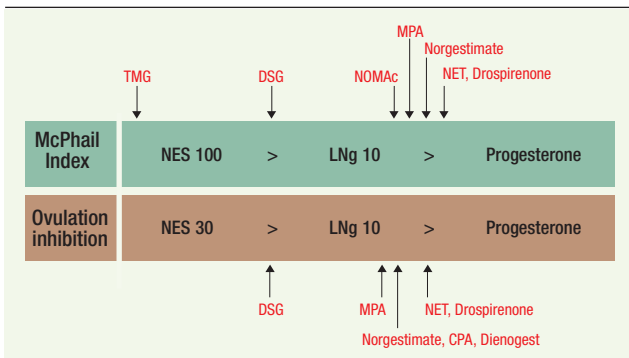


FIGURE 2

Comparative potency of progestogens



CPA, cyproterone acetate; DSG, desogestrel; LNg, levonorgestrel; MPA, medroxyprogesterone acetate; NES, nesterone; NET, norethisterone; NOMAC, norgestrol acetate; TMG, trimegestone. Adapted from Schindler AE, et al. *Maturitas*. 2003;46(suppl 1):S7-S16.

ences of potency into account. Additionally, studies often do not evaluate the effects of progestogens on specific organs or compare the side-effect profiles of individual agents. These characteristics constitute an important, although rarely discussed, aspect of the differences among progestogens. As these characteristics influence an agent's side-effect profile, they are of great importance to clinicians in practice and may affect a clinician's choice of agent for a specific patient.

Route of administration: Bioavailability and systemic effects

The route of administration of progestogens affects their bioavailability and systemic effects. Oral administration is used widely in hormone therapy. Intramuscular (IM) administration has, for many years, been the mainstay of therapy for infertility and assisted reproduction. Intrauterine administration of progestogens is gaining interest with the approval of the levonorgestrel-releasing intrauterine device. Transdermal and vaginally administered products are also available. Current investigations are evaluating the potential of products administered by the intranasal, sublingual, or rectal route.

Potential systemic effects of oral agents

The route of administration may have profound effects on the active metabolism of progestogens, particularly via pathways that influence an agent's side-effect profile. Thus, these effects should be of great interest to clinicians. Most important are the pathways through which orally administered progesterone is transformed into

11-deoxycorticosterone (DOC) and further into the metabolites that form pregnanolone (3 α -hydroxy-5 α -pregnane-20-one) and its isomer allopregnanolone (3 β -20 β -dihydroxy-5 α -pregnane). Allopregnanolone is a very active metabolite of orally administered progesterone that interacts with the gamma-aminobutyric acid (GABA) receptor complex. The resulting actions are similar to those of the benzodiazepines, barbiturates, and other sedatives and hypnotics.

The potential negative effects have been correlated to the extent to which women metabolize progesterone to allopregnanolone. In some women, these metabolites may elicit drowsiness, fatigue, or dizziness. In other individuals, they act as mild anxiolytic and sedative hypnotic agents. For these reasons, oral administration of progesterone is recommended at bedtime. Bedtime administration may reduce the incidence of side effects that "carry over" to the following day. These mild anxiolytic and sedative hypnotic effects may be used therapeutically in perimenopausal and postmenopausal women who have difficulty sleeping.²

Side effects differ among progestogens and are frequently dose-related. Progesterone has an intrinsic antimineralocorticoid (or diuretic) effect, which usually predominates over the effects of DOC in sodium retention of water by the kidneys. These diuretic effects are similar in potency to about 25 mg of spironolactone. However, some patients metabolize more progesterone to DOC, which may result in breast tenderness, edema, and mood changes.³⁻⁵

Synthetic progestins may produce androgenic side effects that can include acne, seborrhea, and darkening of facial hair. Physiologic effects may include anxiety, irritability, depression, somnolence, and mood changes. Serious side effects associated with progestins may include cardiovascular effects, hypertension, clotting, and altered carbohydrate and lipid metabolism. These latter metabolic effects rarely are noted with natural progesterone.⁶

Effects associated with vaginal administration

Progesterone may be administered vaginally in a gel form or by placing the oral micronized progesterone capsule vaginally. This approach has been used therapeutically in Europe for many years.

An abundance of literature demonstrates the selective absorption of vaginally administered progesterone into the uterine circulation.^{7,8} Targeted drug delivery to

the uterus maximizes the desired local effects and minimizes the potential for first-pass systemic side effects following oral administration and metabolism in the liver.

The effect of route of administration (oral versus vaginal) on systemic and local levels of progesterone depending on the route of administration was evaluated by Nahoul et al.⁹ The investigators noted a dramatic difference in serum levels of metabolites, as shown in **FIGURE 3**. Compared with vaginal administration, oral administration resulted in considerably higher levels of all central nervous system active progesterone metabolites. These findings demonstrate the differences in neuroactive steroids associated with oral versus vaginal administration.

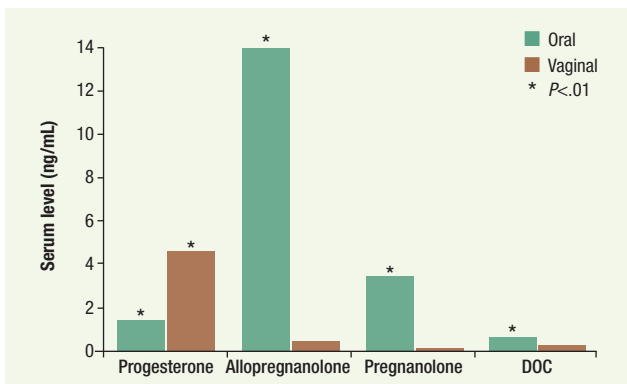
The impact of vaginal versus IM administration has been studied. The serum progesterone levels associated with vaginal and IM administration were evaluated in a randomized open study of 14 women undergoing transabdominal hysterectomies.⁷ For 2 to 4 weeks prior to surgery, women received transdermal estradiol, 0.05 mg/d. Participants then were randomized to receive either an 8% vaginal progesterone gel (90 mg) or IM progesterone injections (50 mg) at 8:00 AM and 8:00 PM on the day before surgery and at 6:00 AM on the day of surgery. Blood samples to assess baseline serum progesterone levels were taken at 8:00 AM on the day before surgery and during the operation.

Serum progesterone levels after vaginal administration were low when compared with serum levels after IM administration. Although the effects observed with IM administration were primarily systemic, the effects of vaginally administered progesterone were largely local. This investigation confirmed earlier work by Miles et al,⁸ who documented better endometrial synchrony in agonadal women using the vaginal delivery of progesterone for endometrial priming in a surrogate embryo transfer program.

Thus, vaginal administration, through insertion of capsules or use of bioadhesive gels, may be an alternative for patients who are intolerant to or experience adverse central nervous system effects from oral formulations, such as excessive sedation, dizziness, negative mood effects, or edema. When progestogen therapy is indicated to manage excessive and/or irregular bleeding, vaginal administration may be recommended because it offers decreased hepatic metabolism and preferentially distributes progesterone to the uterus and target tissue. Patient acceptance, however, is generally lower than with the oral route of administration.^{2,10}

FIGURE 3

Serum metabolite levels of progesterone by route of administration



DOC, 11-deoxycorticosterone.
 Nahoul K, et al. *Maturitas*. 1993;16:185-202.

Conclusion

Clinicians have numerous options in selecting a progestogen for the individual patient. The specific properties of progesterone or synthetic progestins may result in differing side-effect profiles for individual patients. Route of administration also offers differing systemic or local effects that should be considered for some uses and specific patients. These effects should be kept in mind in subsequent discussions of specific uses of progesterone and progestins throughout this monograph.

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Secondary amenorrhea: Uses of progesterone for induction of bleeding

James A. Simon, MD

Progesterone is an established agent that effectively induces bleeding in many patients with secondary amenorrhea. Although all clinicians are familiar with secondary amenorrhea, the condition does not have a precise and universal definition in the medical literature. Thus, it is difficult to compare the results of clinical trials in any meaningful way. Although clinicians generally define secondary amenorrhea as the absence of menstruation for 3 months or 90 days, it also has been defined as amenorrhea of 50 or more days, as bleeding at intervals of 60 days or greater, or as the absence of menses for 6 months or more. In some investigations, the definition also has included oligomenorrhea, defined as blood flow every 35 days to 6 months.

The overall incidence of secondary amenorrhea is 1.8% to 3% among women of reproductive age, but it is significantly higher (7.6%) in women aged 15 to 24 years, declining to 3% in women aged 25 to 34 years and rising slightly to 3.7% in women aged 35 to 44 years. In patients who experience infertility, rates may be as high as 20%.¹

Causes of secondary amenorrhea

Patients with infrequent menstruation should receive a complete history and physical examination to rule out pregnancy. They should be evaluated for possible ovarian failure and pituitary or hypothalamic dysfunction, as well as other potential causes.

Secondary amenorrhea most often is caused by chronic anovulation and hypoestrogenic or euestrogenic states. Most commonly, the condition results from a disruption of the hypothalamic-pituitary-ovarian axis and is characterized by decreased or inconsistent fol-

licle development. Significantly, such patients are also hypoestrogenic and thus may not respond to the administration of progesterone alone.

Secondary amenorrhea also may be caused by insufficient production, release, or coordinated increases in follicle-stimulating hormone and resultant estradiol levels such that a midcycle luteinizing hormone surge does not occur. Without ovulation, no corpus luteum develops and progesterone is not secreted by the ovary, resulting in continuing endometrial proliferation and absence of menses. Long-term consequences can include dysfunctional uterine bleeding, endometrial hyperplasia, and adenocarcinoma.

Secondary amenorrhea may be the result of several medical conditions, including polycystic ovarian syndrome. Therefore, both low and high estrogen states may demonstrate amenorrhea and low progesterone levels. Retained gestational tissue from a known pregnancy, ectopic pregnancy, or incomplete abortion can also cause secondary amenorrhea. Less commonly, secondary amenorrhea may indicate other benign uterine abnormalities such as adenomyosis, endometriosis, polyps, endometritis, infectious diseases, neoplastic lesions, luteal-phase defects, or an abnormal corpus luteum.

Treatment of secondary amenorrhea

Agents approved in the United States to treat conditions associated with secondary amenorrhea are micronized progesterone, progesterone gel, norethindrone acetate, and medroxyprogesterone acetate. The medical literature contains reports evaluating progesterone and progestins delivered orally, vaginally, or intramuscularly at

various dosages. Endpoints have typically included the duration of subsequent amenorrhea, bleeding response, and effect of the treatment on the endometrium. **TABLE 1** summarizes the results of prospective clinical trials of a subset of progestins and progesterone in the treatment of secondary amenorrhea in terms of both the definition of amenorrhea used by the investigators and the effects on bleeding.²⁻⁵

Effects of progesterone gel formulations

Beneficial effects have been reported using progesterone gel formulations. Warren et al⁵ evaluated 127 women with hypothalamic amenorrhea or premature ovarian failure, who were primed with estrogen for 3 cycles as a model for secondary amenorrhea. They received a progesterone gel every other day for a total of 6 doses. Endometrial effects were evaluated after cycle 2 and cycle 3. Withdrawal bleeding occurred in 81% of women treated with the 4% gel and 82% of women treated with the 8% gel. Endometrial effects were noted in 92% of women treated with the 4% gel and 100% of women treated with the 8% gel.

The investigators also assessed psychological symptoms before and during treatment and demonstrated that very few side effects occurred. These findings suggest relatively little metabolism and binding of the progesterone and its metabolites to gamma-aminobutyric acid receptors (**FIGURE 1**).

Oral progesterone administration

Shangold et al³ studied 60 women with secondary amenorrhea to assess the efficacy of oral micronized progesterone at doses of 200 mg and 300 mg. For this study, secondary amenorrhea was defined as a history of oligomenorrhea and current amenorrhea of 50 to 300 days' duration. The outcomes related to endometrial effects and bleeding patterns are shown in **FIGURE 2**. The study authors concluded that progesterone, 300 mg qd, was significantly more effective than placebo in inducing withdrawal bleeding. Surprisingly, the placebo group

TABLE 1

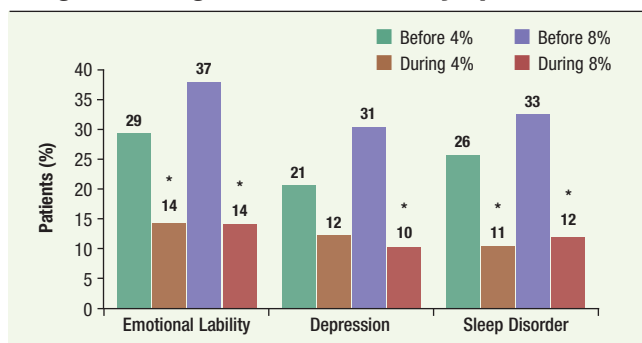
Key studies: Progesterone treatment for secondary amenorrhea

| Author, Year | N | Agent | Duration of Amenorrhea | Bleeding Response (%) |
|-----------------------------|-----|---|---|--|
| Kletzky, 1975 ² | 90 | IM progesterone: 100 mg, 200 mg | 6 months | 70 (both doses combined; 63/90) |
| Shangold, 1991 ³ | 60 | MP: 200 mg, 300 mg Pbo | 50-300 days | 300 mg: 90 200 mg: 58 Pbo: 29 |
| Battino, 1996 ⁴ | 48 | MPA: 5 mg BID DG: 10 mg BID | 50 days | MPA: 95 DG: 92 |
| Warren, 1999 ⁵ | 127 | Progesterone gel: 45 mg, 90 mg | 6 months | 45 mg: 81 90 mg: 82 |
| Archer, 2000 | 107 | MP: 100 mg, 200 mg, 300 mg, 400 mg Pbo | Postmenopausal (artificial menstrual cycle induced) | 100 mg: 55 200 mg: 81 300 mg: 74 400 mg: 91 Pbo: 9 |

DG, dydrogesterone; IM, intramuscular; MP, micronized progesterone; MPA, medroxyprogesterone acetate; Pbo, placebo. Kletzky OA, et al. *Am J Obstet Gynecol.* 1975;121:695-703; Shangold MM, et al. *Fertil Steril.* 1991;56:1040-1047; Battino S, et al. *Gynecol Obstet Invest.* 1996;42:113-116; Warren MP, et al. *Am J Obstet Gynecol.* 1999;180(1 Pt 1):42-48; Archer DF. Oral communication, January 2007.

FIGURE 1

Treatment of secondary amenorrhea: Progesterone gel use and mood symptoms



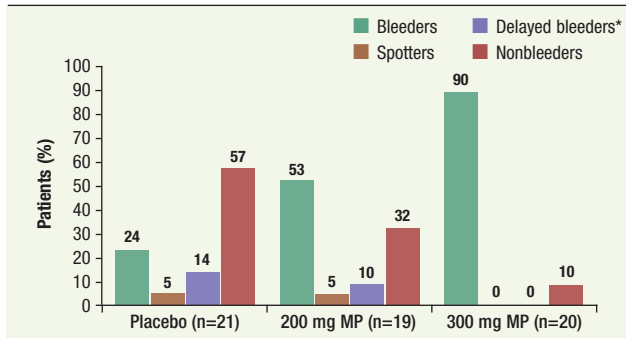
Administration of 4% or 8% progesterone gel.
 *Corresponding P-values <.05 when compared with before treatment.
 Warren MP, et al. *Am J Obstet Gynecol.* 1999;180(1 Pt 1):42-48.

showed significant improvements, although there appeared to be no threshold for progesterone concentrations above which women always bled and below which they never bled. Side-effect profiles, shown in **FIGURE 3**, were similar among both treatment arms and the placebo group. No significant changes in lipid concentrations were observed during the short-term treatment.

Of particular note is the 2000 study by Archer et al (personal communication) that eliminated issues of natural cycling. In this trial, the US Food and Drug Administration allowed the investigators to create a model of secondary amenorrhea using estrogen-

FIGURE 2

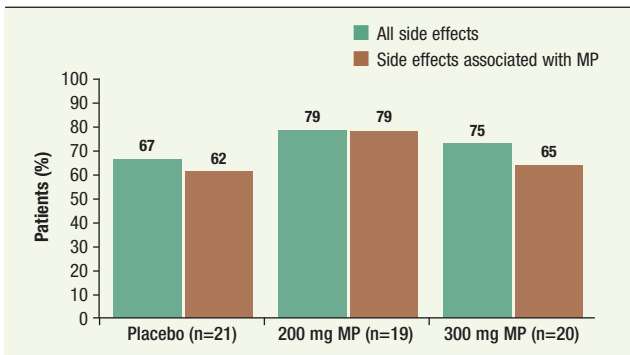
Bleeding induction: Oral progesterone



* $P < .0002$ versus placebo.
 MP, micronized progesterone.
 Delayed bleeders defined as "onset of bleeding >16 days after initiating therapy."
 Shangold MM, et al. *Fertil Steril.* 1991;56:1040-1047.

FIGURE 3

Progesterone: Side effects of oral administration



No significant differences in TC, TG, HDL, and LDL when compared with baseline values in all 3 study arms.
 HDL, high-density lipoprotein; LDL, low-density lipoprotein; MP, micronized progesterone; TC, total cholesterol; TG, triglycerides.
 Shangold MM, et al. *Fertil Steril.* 1991;56:1040-1047.

TABLE 2

Progesterone: Induction of bleeding

| Withdrawal bleeding (cycle 3), % | |
|---|----|
| Micronized progesterone, 300 mg/d, 10 days: | 74 |
| Micronized progesterone, 400 mg/d, 10 days: | 91 |
| Placebo group: | 9 |

DF Archer, MD, oral communication, January 2007.
 Prometrium [prescribing information]. Marietta, GA: Solvay Pharmaceuticals, Inc; 2004.

primed menopausal women with an intact uterus. Thus, this study regimen created an artificial menstrual cycle for participants, who received dosages of progesterone ranging from 100 to 400 mg/d with conjugated equine estrogens, 0.625 mg/d, "endometrial priming." The primary endpoint was the incidence of endometrial secretory transformation, with incidence of withdrawal bleeding also of importance.

This study was one of those that formed the basis for the FDA-approved 400-mg dosage of oral micronized progesterone for secondary amenorrhea. The 400-mg dosage produced a significantly higher rate of withdrawal bleeding (TABLE 2) compared with lower dosages. Additionally, the 400 mg/d dosage resulted in a significantly greater rate of complete secretory activity of the endometrium (64%) versus placebo (0%). Therefore, the FDA concluded that a single daily dose of micronized progesterone of 400 mg, administered in the evening for 10 days, is the appropriate dosage for secondary amenorrhea.

Conclusion

Secondary amenorrhea is common and a variety of treatments may induce bleeding. Progesterone and progestin therapy have demonstrated short-term benefits. It should be noted that all agents that contain progestogens are efficacious; the primary distinctions among agents involve the side-effect profiles, as well as effects of dosage and route of administration.

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Progesterone: Uses in ART and prevention of pregnancy loss

Marcelle I. Cedars, MD

For some women, exogenous progesterone administration may be necessary to maintain pregnancy, whether it is administered to improve fertility, prevention of recurrent pregnancy loss, or to provide support in assisted reproduction. This article will describe the uses of progesterone during pregnancy.

Luteal-phase defect and progesterone

Progesterone, as well as clomiphene citrate, aromatase inhibitors, and gonadotropin, is often used to improve luteal function, with potential benefits for fertility and prevention of recurrent pregnancy loss. This agent has specific effects on hormonal levels at the follicular phase or the luteal phase, or both, through a variety of actions.

Luteal-phase defect is, essentially, a progesterone-deficiency defect that is best characterized as a subtle form of ovulatory dysfunction. This description is particularly meaningful as it applies to the typical patient who is subfertile and demonstrates clinical characteristics that suggest deficient progesterone production: advanced age, low body weight, and/or shortened menstrual cycles that are often accompanied by premenstrual spotting. Additionally, it should be noted that the use of ovulation-induction methods may compromise the luteal phase.

The impact of a patient's age on luteal function is clear. The relationship between age and luteal function also sheds light on the entire process by which luteal-phase defect, or insufficiency, occurs: In older women, the levels of progesterone metabolites are reduced significantly during the luteal phase, even in women with "regular" cycles.¹ Women who have regular menstrual cycles should be suspected of having luteal-phase defect if they have a history of shortened intermenstrual inter-

vals and premenstrual spotting, characteristics that suggest premature breakdown of the endometrium because of lack of support from progesterone. This population also may show an increase in premenstrual symptoms that may be characterized as new-onset symptoms.

Estrogen levels in this older group also may not have the pronounced luteal-phase peak that occurs in younger women (preliminary data, Cedars). This change in estrogen secretion levels actually may initiate much of the luteal-phase deficiency process by promoting defective folliculogenesis. Therefore, luteal-phase defect may actually be viewed best as a continuum of defective ovulation.

Strategies to extend the luteal phase

Various agents are used to extend the luteal phase and increase the likelihood of implantation. Clomiphene citrate (CC), a selective estrogen-receptor modulator, is administered to establish a normal ovulatory cycle and extend the luteal phase by increasing levels of endogenous progesterone. It also increases the levels of endogenous estradiol, perhaps as a result of its effects on multifollicular development. Thus, it is an effective agent for improving fertility in specific groups of patients who have normogonadotrophic and normoestrogenic ovulatory dysfunction.

Several small studies provide important clues to guide clinicians in the use of this agent. An early study by Daly and Riddick² evaluated the effects of CC administered during the follicular phase compared with the use of luteal-phase progesterone in women with biopsy-diagnosed luteal-phase defect. The more severe the defect, the greater benefit seen with CC compared with the benefits of luteal-phase progesterone. This supports

TABLE 1
Luteal-phase function: Letrozole versus clomiphene citrate

| | Letrozole | Clomiphene Citrate |
|---|---------------|--------------------|
| Total number of follicles | 5.5 ± 0.4 | 4.8 ± 0.3 |
| Number of follicles larger than 14 mm | 2.0 ± 0.1 | 1.7 ± 0.1 |
| Number of dominant follicles | 1.3 ± 0.1 | 1.1 ± 0.1 |
| Pretreatment endometrial thickness (mm) | 4.4 ± 2.2 | 4.5 ± 0.2 |
| Endometrial thickness at hCG (mm) | 7.1 ± 0.2 | 8.2 ± 0.6 |
| Duration of stimulation (d) | 10.1 ± 0.3 | 10.8 ± 0.9 |
| Pregnancy (%) | 11.5 (13/115) | 8.9 (11/123) |
| Spontaneous abortion (%) | 0 (0/115) | 36 (4/11) |
| On-going (%) | 9.6 (11/115) | 6.5 (8/123) |

hCG, human chorionic gonadotropin.
Al-Fozan H, et al. *Fertil Steril*. 2004;82:1561-1563.

the theory that the actual defect began in the follicular phase. Creus³ and Ordi⁴ reported no adverse effect on integrin, leukemia inhibitory factor, or E-cadherin with CC. A reduction in pinopode formation was noted. The work by Ordi⁴ suggests reproducibility of these markers is poor, thus limiting their usefulness.

In a 2005 study, Palomino et al⁵ evaluated CC's effect on estradiol and progesterone levels, as well as on endometrial epithelial integrins and progesterone receptors during the luteal phase of 31 fertile women. The investigators noted that this agent was associated with β³-integrin abnormalities, although no differences were associated with in-phase biopsies. Thus, CC may affect the expression of markers of endometrial receptivity and cause a failure in the luteal function, despite high plasma levels of progesterone. Randomized controlled trials have not been conducted to confirm this.

Aromatase inhibitors also are used to treat luteal-phase dysfunction and recurrent pregnancy loss; small trials have compared the effects of CC and these agents on pregnancy rates. Recently, 15 patients having intrauterine insemination received either letrozole, 2.5 mg (n = 7), or CC, 100 mg (n = 8), from day 3 to day 7 of the cycle.⁶ Intrauterine insemination was performed 1 day after confirmation of LH peak. No luteal support was administered. Significantly higher levels of estradiol and progesterone—as well as a higher number of dominant follicles—developed in patients in the CC group compared with those in the letrozole group.

Al-Fozan et al⁷ compared the effects of letrozole and CC on pregnancy outcomes in women with idiopathic

infertility who were undergoing superovulation and intrauterine insemination over a total of 238 cycles. No significant differences were reported in the total number of developing follicles and endometrial thickness. Pregnancy rates per cycle associated with the use of CC and letrozole were similar (8.9% and 11.5%, respectively); however, 4 of the 11 pregnancies in the CC group resulted in a spontaneous abortion (36.6%) (TABLE 1). It is unclear whether the results of such a small study can be applied broadly; clinicians, therefore, should assume that there are no differences between treatment with CC and with letrozole.

Exogenous progesterone and hCG inhibit cell apoptosis

The use of human chorionic gonadotropin (hCG) and exogenous progesterone may prolong the health of the luteal phase in women with infertility or recurrent pregnancy loss. Significantly, the use of these agents has been associated with decreased cellular apoptosis, which may be important in preserving endometrial function, prolonging the health of luteal phase, and thus promoting implantation. In a 2005 controlled, prospective, and randomized study, Lovely et al⁸ examined the effects of exogenous hCG and progesterone on apoptosis in late luteal-phase endometrial biopsies of 12 healthy fertile women (aged 20 to 34 years) with regular menstrual cycles. The women received luteal doses of either intravaginal progesterone, 200 mg (on days 18 to 27), or a single IM injection of hCG, 10,000 IU, on day 19. At 26 days, a second endometrial biopsy was performed and serum was collected. Evidence of apoptosis was reduced significantly with both luteal-phase treatments. Serum progesterone levels were higher in the hCG-treated group; however, the difference between groups was not statistically significant. These findings suggest that luteal-phase support may prolong the health of the luteal phase in part by preventing programmed cell death.

Progesterone: Route of administration

Progesterone can be administered by the oral, vaginal, or IM route. Absorption based on route of administration was evaluated in 2 very small studies conducted in the early 1990s (FIGURE 1). In the study shown on the left panel, Nahoul et al⁹ evaluated plasma progesterone after

oral or vaginal administration of progesterone in 6 premenopausal women. Micronized progesterone, 100 mg, was administered vaginally and orally in the luteal phase of the menstrual cycle. In the second cycle, the same doses were administered, but by different routes. As shown in **FIGURE 1**, circulating progesterone levels were higher after vaginal administration than after oral administration. Miles et al¹⁰ enrolled 4 normally ovulating women and 20 functionally agonadal women receiving estrogen replacement. Participants received micronized progesterone administered either vaginally or by twice-daily IM injections. Although serum levels were higher with IM administration, vaginal administration demonstrated higher levels in the target tissue.

Progesterone and recurrent pregnancy loss: Immunologic effects

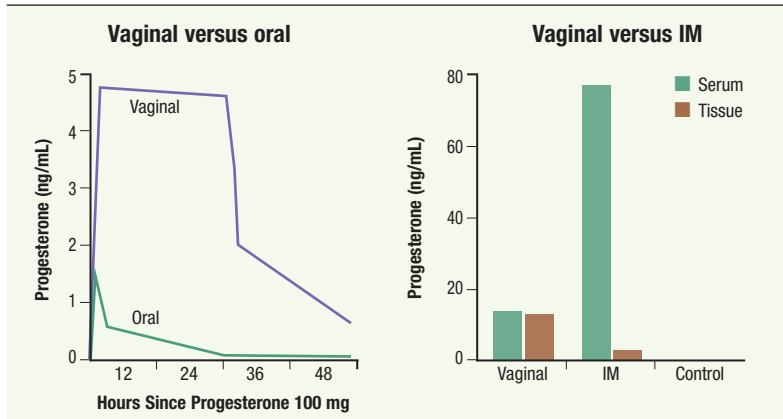
Certainly, endogenous progesterone, as has been discussed, is essential for supporting a pregnancy and has significant direct effects. A pregnancy will fail if a progestogen antagonist is administered or if surgery is performed to remove a hemorrhagic corpus luteum. However, it is likely that progesterone also exerts nonhormonal immunologic effects. We know that progesterone induces an immunomodulatory-blocking factor critical in suppressing T-helper 1 cytokines and thus exerting antiabortive effects. In the first trimester of pregnancy, the ratio of T-helper 1 to T-helper 2 cytokines is critical. The relation between these cytokines, and potential effects on spontaneous abortion, has been examined.

Raghupathy¹¹ studied the associations of cytokine expression of T-helper 1, 2, and 3 cytokines and the mechanisms that may be associated with immunologically mediated pregnancy failure. Secretion of transforming growth factor- β by T-helper 3 cells also may play a role. A strong association between maternal T-helper 2-type immunity and successful pregnancy was reported in this study, as was an association between T-helper 1-type and pregnancy loss.

To underscore this point, the ratio of mean cytokine levels between these 2 cytokines in women who have normal pregnancies or recurrent loss is shown in **FIGURE 2**.

In 2005, Gruber and Huber¹² reviewed the evidence

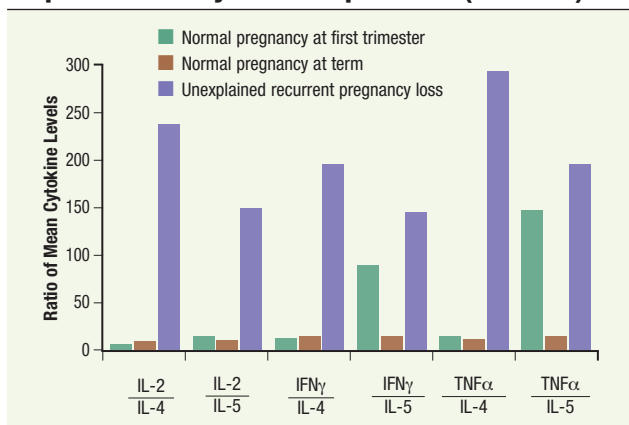
FIGURE 1
Progesterone absorption: Effects of routes of administration



Nahoul K, et al. *Maturitas*. 1993; 16:185-202.

Miles RA, et al. *Fertil Steril*. 1994;62:485-490.

FIGURE 2
Recurrent pregnancy loss: Importance of cytokine expression (Th1/Th2)



Raghupathy R. *Semin Immunol*. 2001;13:219-227.

regarding the administration of progesterone and dydrogesterone in the prevention of habitual abortion. When peripheral mononuclear cells from women who have recurrent pregnancy loss were incubated with progesterone or dydrogesterone in vitro, T-helper 1 cytokine interferon-gamma decreased, while T-helper 2 cytokines such as interleukin-4 and interleukin-6 markedly increased, further documenting the importance of this cytokine ratio.

The literature regarding recurrent pregnancy loss and the efficacy of progesterone was evaluated in a 2003 Cochrane collaboration review by Oates-Whitehead et al.¹³ The investigators reviewed 30 original

studies, of which 14 met criteria for further review. Overall, the data showed that progesterone reduced the risk of miscarriage in women with recurrent losses, not in threatened loss.

Progesterone in assisted reproduction technologies: Luteal-phase support

Finally, progesterone is used in fertility care with ART. Certainly, adequate levels of progesterone are essential to support implantation and early pregnancy. However, both the procedures used in ART and the agents administered to induce ovulation and stimulate the ovaries may interfere with progesterone production. How critical is administration of exogenous progesterone? Are the route of administration and the specific properties of available agents of consequence?

Endogenous levels of progesterone may well be insufficient: at the time of oocyte retrieval, aspiration of follicles may result in the removal of granulosa cells. Therefore, levels of luteal-phase progesterone may not be adequate to support the endometrium and early pregnancy. Administration of other agents, such as gonadotropin agonists alone or with CC, also may be associated with diminished or defective progesterone production during the luteal phase. The reasons for this effect remain unclear; however, possible causes may include excessively high estradiol levels during the follicular phase and suppression of endogenous luteinizing hormone following administration of hCG, early induction of progesterone receptors, or negative impact on cytosolic progesterone receptors. Conversely, gonadotropin-releasing hormone (GnRH) antagonists are shorter-acting and it has been thought that they will not result in defective luteal function. The lower levels of follicular phase estrogen also might be a benefit.

Early studies suggested that progesterone support in the luteal phase was unnecessary.¹⁴ In these investigations, addition of agonists led to a fall in luteal-phase progesterone and premature luteolysis. However, since it has been shown that without luteal-phase support, either through hCG (increasing endogenous progesterone) or administration of exogenous progesterone, pregnancy rates are reduced.

A recent study by Beckers et al¹⁵ looked at GnRH antagonist cycles to evaluate premature luteal phase in patients with ovulation induction with recombinant follicle-stimulating hormone combined with a

GnRH antagonist. Ovulatory trigger was initiated by recombinant-hCG (r-hCG), recombinant luteinizing hormone, or GnRH agonist. No luteal support was provided, and the median duration of the luteal phase was 13, 10, and 9 days, respectively. The least disruption to the luteal phase was seen in the r-hCG group, probably because of slow clearance of hCG from the circulation, which extended luteal support of the corpus luteum. Despite high progesterone and estradiol concentrations in the early luteal phase, luteolysis began prematurely, probably as a result of excessive negative feedback stemming from suppressed release of pituitary LH. The study was stopped early because of the low pregnancy rate and very obvious premature luteolysis. Clearly, luteal-phase support of ART cycles is critical to success.

The question remains: What is the best method for providing luteal-phase support during an ART cycle? In the Cochrane Database review by Daya et al,¹⁴ a comparison of placebo versus hCG demonstrated the importance of luteal-phase support. A comparison of studies revealed no difference in efficacy between hCG, which stimulates the production of progesterone, and the administration of exogenous progesterone for luteal-phase support. Given the higher risk of ovarian hyperstimulation syndrome associated with luteal-phase hCG support, progesterone support is preferable (TABLE 2).

Progesterone: Route of administration

A study by Chakravarty et al¹⁶ compared vaginal administration of micronized progesterone to oral delivery of dihydroprogesterone, a form of progesterone not available in the United States. The study results indicate that the viable delivery rates (22.8% and 24.1%, respectively), and the spontaneous abortion rates (8.3% and 7.6%, respectively) were similar in both groups.

As Dr Simon noted in his introductory comments, route of administration is important, but so are the molecular absorption dynamics and bioavailability of agents. Whereas most studies have suggested no difference between the use of IM and vaginal routes of administration on pregnancy outcome, it is hypothetically possible that the very high local levels and rapid absorption associated with vaginal administration may shorten the window of implantation by accelerating the progesterone response of the endometrium. The proper timing

and dosing may not be known at this time.

There seem to be similar outcomes for ongoing pregnancy associated with both progesterone capsules and gel formulations. Kleinstein et al¹⁷ noted similar rates of ongoing pregnancy with vaginal progesterone capsules compared with a vaginal 8% gel, with pregnancy rates of 25.2% versus 22.2%, respectively. Additionally, data suggest that patients may accept vaginal delivery versus IM delivery of agents more readily.

Conclusion

Some women may have inadequate amounts of progesterone and may have inadequate luteal phases, although the only means of diagnosis currently available are a patient history and assessment of hormonal factors that suggest dysfunctional folliculogenesis. At-risk women include those with diminished ovarian reserve and/or decreased estradiol levels, suggesting the importance of the follicular phase in identifying and treating defective luteal-phase function.

In the treatment of recurrent pregnancy loss, there is a suggestion that progesterone is helpful in women who have otherwise unexplained recurrent pregnancy loss; however, the indications and mechanisms are unclear.

In ART, the administration of endogenous progesterone for progesterone support is required. It appears that the use of progesterone alone is likely adequate: vaginal, IM, or oral (in the case of dydrogesterone only) administration appear to be equally effective.

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TABLE 2

hCG versus progesterone: Summary of studies

| | Progesterone | Placebo | Fixed Odds Ratio 95% CI | Weight | Fixed Odds Ratio (95% CI) |
|-----------------------|--------------|------------|----------------------------|--------------|------------------------------|
| No GnRH-a | | | | | |
| Kupfermanc (1990) | 13/54 | 10/51 | | 8.7 | 1.30 (0.51, 3.30) |
| Yovich (1984) | 2/17 | 3/17 | | 2.9 | 0.62 (0.09, 4.29) |
| Yovich (1991) | 13/50 | 14/55 | | 11.0 | 1.03 (0.43, 2.47) |
| Subtotal (95% CI) | 121 | 123 | | 32.6 | 1.08 (0.59, 1.97) |
| With GnRH-a | | | | | |
| Araujo (1994) | 10/34 | 12/35 | | 9.3 | 0.80 (0.29, 2.20) |
| Claman (1992) | 4/29 | 10/72 | | 8.3 | 0.55 (0.16, 1.87) |
| Golan (1993) | 1/26 | 6/30 | | 6.0 | 0.16 (0.003, 1.43) |
| Ludwig (2001 - low) | 8/70 | 11/77 | | 10.3 | 0.77 (0.29, 2.05) |
| Martinez (2000) | 54/168 | 41/142 | | 33.6 | 1.17 (0.73, 1.90) |
| Van Steroghorn (1988) | 39/193 | 11/41 | | 10.0 | 0.96 (0.38, 2.44) |
| Subtotal (95% CI) | 397 | 397 | | 77.4 | 0.90 (0.64, 1.27) |
| Total (95% CI) | 518 | 520 | | 100.0 | 0.94 (0.70, 1.27) |

GnRH-a, gonadotropin-releasing hormone agonist.
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Progesterone and progestins in postmenopausal hormone therapy

Robert D. Langer, MD, MPH

Progestogens used as agents in combined hormone therapy (HT) offer only 1 benefit: They provide essential protection against estrogen-induced endometrial hyperplasia and cancer in women with a uterus. Clinical trials have shown that progestogens provide no meaningful increase in estrogen's benefits to bone. However, progestins may attenuate estrogen's beneficial effects on lipids and blood flow.

Side effects associated with progestogen use include bloating, irritability, and breast tenderness. Progestogens induce vaginal bleeding, although the likelihood of spotting or breakthrough bleeding varies by dosing pattern and agent.

As Dr Simon noted in his introduction, progestogens vary in their potency, biochemical characteristics, side-effect profile, and recommended use. So the primary clinical question is: What are the specific properties and effects of currently available agents? What is the impact of potential side effects on patient compliance? Which agent and dosing regimen is the best choice for a specific patient? Perhaps most important, what do the current data show regarding the risks and benefits of HT? What part do progestogens play in these risks and benefits?

The PEPI Trial: Pivotal findings and implications for practicing clinicians

Much of the best comparative data about agents used in HT has been derived from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. This investigation was one of the first long-term studies to compare the progestogens and evaluate their specific

effects. Indeed, it was the first large clinical trial in which women were randomized to all treatment arms regardless of whether or not a particular patient had a uterus. This 3-year study, sponsored by the National Heart, Lung, and Blood Institute, was a head-to-head randomized controlled trial analyzing a variety of regimens combining estrogen and progestogen. The robust data from this trial remain of use to clinicians in practice and offer a rare look at the comparative effects of widely used regimens.¹

The PEPI study was designed to evaluate biological mechanisms that could mediate cardiovascular benefits suggested by earlier observational studies. Both the Framingham Heart Study and the Lipid Research Clinics Follow-up Study^{2,4} had implicated high serum levels of low-density lipoprotein cholesterol (LDL-C) as a risk factor for cardiovascular disease. Perhaps more importantly, these investigations had also shown that high levels of high-density lipoprotein cholesterol (HDL-C) were associated with lower coronary heart disease (CHD) risk, and that the HDL-C effect was stronger in women than men. Data available when PEPI was designed also indicated that clotting factors, such as fibrinogen, and insulin resistance were associated with increased cardiovascular risk. The latter effect was so powerful that it neutralized the usual age-specific advantage of female gender for coronary risk. Last, there was some question regarding whether HT increased blood pressure. PEPI was designed to evaluate the impact of HT on these cardiovascular risk factors and to compare simultaneously the effects of several HT regimens on endometrial safety, bone, and quality of life.

The progestogens in PEPI were selected to include the regimens likely to be in common use when the study was completed. Cyclic medroxyprogesterone acetate (MPA) was the dominant treatment at that time, with good evidence for endometrial protection. The investigators wanted to test the efficacy of continuous MPA, which was then emerging as an alternative used to minimize some side effects. Micronized progesterone (MP) was potentially more physiologic, because it was identical metabolically to endogenous progesterone. It had been used in Europe but was not available in the United States. Given concerns that progestogens could neutralize potential benefits of estrogens, the investigators elected to test MP to determine if it differed meaningfully from the synthetic alternatives. The PEPI study provided key supporting data for the US Food and Drug Administration approval of MP and was pivotal in demonstrating the safety of continuous MPA administration.

The 4 active treatment groups and the placebo group each enrolled 175 women. All active regimens used conjugated equine estrogens (CEE) 0.625 mg/d. One group received unopposed CEE, and 1 group received placebos for the both estrogen and progestogen components. There were 3 combination treatment arms with CEE plus 1 of the following progestogens: MP, 200 mg, 12 d/mo; MPA, 2.5 mg/d continuously; or MPA, 10 mg, 12 d/mo.

Randomization was identical for women with or without a uterus. Participants were followed with clinic visits every 6 months for 3 years. They also kept a daily diary to record a variety of other outcomes. Secondary outcomes included endometrial histology, bone mineral density, and quality of life.

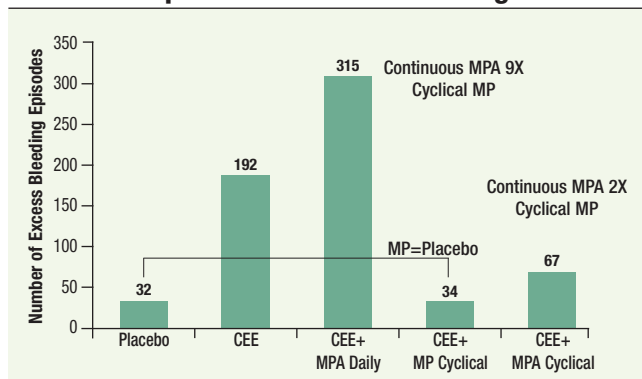
Endometrial safety, bleeding patterns, and compliance

Women with a uterus who received unopposed estrogen had a 20% to 25% annual incidence of hyperplasia. Conversely, all 3 combination regimens were equally protective in preventing estrogen-associated endometrial disease.⁵

Research has established that most women determine whether they will stay on HT based on their experience during the first 6 months. Bleeding patterns and breast symptoms are key factors in these decisions. The PEPI participants kept a daily diary to record bleeding patterns and other side effects. Data on bleeding pat-

FIGURE 1

PEPI Trial: Episodes of excess bleeding



CEE, conjugated equine estrogens; MP, micronized progesterone; MPA, medroxyprogesterone acetate. Lindenfield EA, Langer RD. *Obstet Gynecol.* 2002;100:853-863.

terns were published in 2002 (FIGURE 1), several years after the primary results.⁶ These data are important for practicing clinicians: Women may be more likely to continue treatment with an agent associated with minimal side effects in these areas.

The PEPI results showed that, in the first 6 months, the use of cyclical or continuous MPA was associated with significantly more bleeding than cyclical MP. After the first 6 months, continuous MPA was associated with reduced levels of bleeding, although unexpected breakthrough bleeding continued to be relatively common. At 3 years, the lowest duration of bleeding was associated with continuous MPA, followed by MP, and then by cyclic MPA.

The number of unanticipated bleeding episodes with MP was similar to that of placebo. Episodes of unanticipated bleeding were 9 times more frequent with continuous MPA than with cyclical MP. Unanticipated bleeding was twice as common with cyclical MPA as with MP.

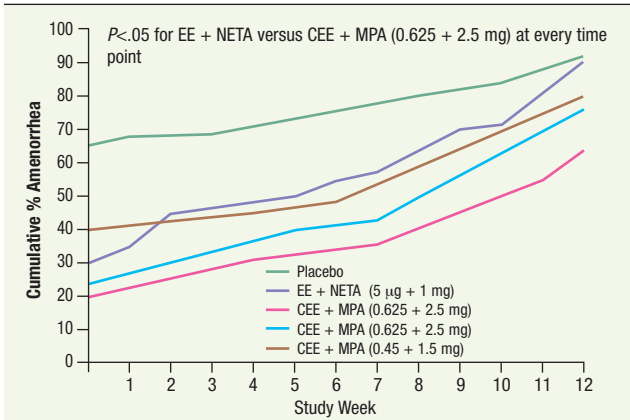
Data from another study comparing bleeding patterns of CEE/MPA and ethinyl estradiol/norethindrone acetate (NETA) also demonstrated more breakthrough bleeding with MPA, although both progestogens produced more initial breakthrough bleeding than was seen with placebo⁷ (FIGURE 2).

Health risks and benefits of HT

Although it is the fear of breast cancer that often drives patients' decisions as to whether to initiate HT, coronary and cardiovascular disease remains the most common cause of mortality for postmenopausal women in the

FIGURE 2

Bleeding associated with HT regimens using MPA or NETA



CEE, conjugated equine estrogens; EE, ethinyl estradiol; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate.
Simon JA. *Am J Obstet Gynecol.* 2003;188:92-99.

United States. In any treatment or intervention for this population, the potential risks and benefits must be evaluated as they apply to an individual patient's risk. Data from the National Center for Health Statistics demonstrate that the risks of breast cancer are quite small when compared with the risk of cardiovascular disease.⁸

The Women's Health Initiative (WHI) clinical trial of HT was intended primarily to test whether treatment begun at ages well beyond menopause would reduce the risk of coronary disease.⁹ The women enrolled were, on average, 63 years old and 12 years postmenopausal. Seventy percent of participants were older than 60 years. This design was built on results from prior observational studies and shorter clinical trials that principally included women who started hormones near the time of menopause. The WHI design assumed that, because older women were at higher risk than younger women, benefits would be at least as great in an older population.

Recent analyses of the WHI data: Effect of HT regimens on newly menopausal women

Recent analyses of the data from WHI age subgroups provide important information about coronary risk for patients who start on HT near the time of menopause. The primary results in the estrogen-alone trial of the WHI (which used .625 mg daily conjugated equine estrogens [CEE]) found that participants aged 50 to 59 years at the start of the study

(n=1637 in the active treatment arm) had a marginal reduction in myocardial infarction, the primary stipulated outcome in the study design. However, when coronary revascularization was included, women who were 50 to 59 years old when they started on the estrogen-only regimen had a statistically significant 34% reduction in coronary events (TABLE 1).¹⁰ This reduction is consistent with the findings of the many observational trials that preceded the WHI and supports many years of clinical practice. This same analysis found that CEE treatment was neither beneficial nor harmful for the same composite coronary outcome in women who were aged 60 to 79 years when they entered the WHI hormone trial.

The take-home message from this subset of the WHI findings is that estrogen therapy begun within the first 10 years of menopause may reduce coronary risk. Beyond the first decade after menopause, the use of estrogen alone is neutral for this outcome. The suggestion that estrogen/progestin HT is associated with reduced cardiovascular risk when administered within 10 years of menopause was also borne out in a 2003 report by Manson et al.¹¹ In that report, HT was not associated with an increase in coronary events for women who were less than 10 years postmenopausal when they entered the study. (The WHI estrogen-alone trial tested CEE, .625 mg daily; the estrogen-plus-progestin trial tested CEE, .625 mg, plus MPA, 2.5 mg daily.)

There was a modest (approximately 10%) reduction of events in those participants that was not statistically significant. The small number of women in this younger age group, however, did provide limited statistical power for this test. The key point is that, for women enrolled in WHI who were within 10 years of menopause when they started in the CEE-plus-MPA study, administration of HT demonstrated no coronary harm and the results implied a possible small coronary benefit. This effect clearly disappeared with increasing age for women 60 years and older.

Additionally, the CEE-plus-MPA trial suggested that vasomotor symptoms are a good marker for estrogen deficiency. An analysis limited to women aged 50 to 59 years when they enrolled suggested that those with vasomotor symptoms had no increased risk of coronary events if treated with CEE plus MPA; in contrast, asymptomatic women in the treatment group in the

TABLE 1

WHI estrogen-only arm: CHD outcomes including revascularization

| Coronary Event | No. of cases (annualized %) by age at baseline, y | | | | | | | | | P Value for interaction |
|--|---|------------------|-------------------------|--------------|------------------|-------------------------|--------------|------------------|-------------------------|-------------------------|
| | 50-59 years | | | 60-69 years | | | 70-79 years | | | |
| | CEE (n=1637) | Placebo (n=1673) | HR (95% CI) | CEE (n=2387) | Placebo (n=2465) | HR (95% CI) | CEE (n=1286) | Placebo (n=1291) | HR (95% CI) | |
| CHD (MI or coronary death) | 21 (0.17) | 34 (0.27) | 0.63 (0.36-1.08) | 96 (0.57) | 106 (0.61) | 0.94 (0.71-1.24) | 84 (0.96) | 77 (0.86) | 1.11 (0.82-1.52) | .07 |
| CABG or PCI | 29 (0.24) | 52 (0.42) | 0.55 (0.35-0.86) | 129 (0.77) | 130 (0.75) | 0.99 (0.78-1.27) | 95 (1.08) | 94 (1.060) | 1.04 (0.78-1.39) | .09 |
| Hospitalized angina | 42 (0.35) | 51 (0.41) | 0.81 (0.54-1.22) | 125 (0.75) | 122 (0.71) | 1.06 (0.82-1.36) | 98 (1.12) | 89 (1.00) | 1.10 (0.82-1.46) | .37 |
| Confirmed angina* | 21 (0.17) | 35 (0.28) | 0.59 (0.34-1.02) | 80 (0.48) | 80 (0.46) | 1.03 (0.76-1.41) | 62 (0.71) | 56 (0.63) | 1.12 (0.78-1.60) | .18 |
| Acute coronary syndrome† | 56 (0.46) | 73 (0.59) | 0.76 (0.54-1.08) | 185 (1.11) | 187 (1.08) | 1.01 (0.82-1.24) | 154 (1.76) | 141 (1.58) | 1.10 (0.87-1.38) | .18 |
| MI, coronary death, CABG, and PCI | 42 (0.35) | 65 (0.52) | <u>0.66 (0.44-0.97)</u> | 177 (1.06) | 177 (1.02) | 1.02 (0.83-1.25) | 137 (1.56) | 130 (1.46) | 1.08 (0.85-1.38) | .09 |
| MI, coronary death, CABG, PCI, and hospitalized angina | 65 (0.54) | 84 (0.68) | 0.78 (0.56-1.07) | 225 (1.35) | 228 (1.32) | 1.01 (0.84-1.21) | 176 (2.01) | 164 (1.84) | 1.08 (0.87-1.34) | .13 |
| MI, coronary death, CABG, PCI, and confirmed angina | 46 (0.38) | 70 (0.56) | <u>0.66 (0.45-0.96)</u> | 186 (1.11) | 194 (1.12) | <u>0.98 (0.80-1.20)</u> | 148 (1.69) | 141 (1.58) | <u>1.05 (0.84-1.33)</u> | .11 |

CABG, coronary artery bypass grafting; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, nominal confidence interval; HR, nominal hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

*Confirmed angina requires hospitalization for angina with confirmatory stress test or obstructive coronary disease by angiography.

†Acute coronary syndrome includes myocardial infarction and hospitalized angina.

Hsia J, et al. *Arch Intern Med.* 2006;166:357-365.

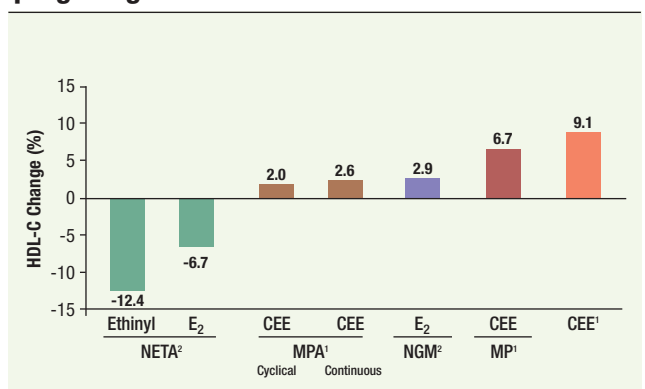
same age range had a 2-fold increase compared with placebo. This contrast did not reach statistical significance, most likely due to the small number of women in this age range. Nevertheless, the magnitude of the contrast suggests that this combination should be considered primarily for symptomatic patients and underscores the labeled indication for HT.

Potential lipid effects of HT

PEPI evaluated the effects of 4 different HT regimens on HDL-C (FIGURE 3). This is the best single lipid predictor of cardiovascular risk in women, although LDL-C also is useful. Each 1 mg/dL change in HDL-C is associated with about a 3% 10-year change in coronary heart disease (CHD) risk, while each 1 mg/dL change in LDL-C is associated with about a 1% difference in 10-year risk. For that reason, the best way to evaluate lipid risk in postmenopausal women is to assess the total cholesterol/HDL-C ratio, with a goal of a ratio lower than 4.

FIGURE 3

Effects on HDL-C: Potency of various progestogens used in HT



CEE, conjugated equine estrogens; E₂, estradiol; HDL-C, high-density lipoprotein cholesterol; HT, hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone acetate; NETA, norethindrone acetate; NGM, norgestimate.

¹The Writing Group for the PEPI Trial. *JAMA.* 1995;273:199-208.

²Full prescribing information for estradiol/norgestimate, 17β-estradiol/ norethindrone acetate, and norethindrone acetate/ethinyl estradiol.

Good levels of HDL-C are critical to achieving a good ratio and reducing cardiovascular disease risk.

In PEPI, mean changes in HDL-C were affected by choice of progestogen and duration of administration. Although all treatment arms were associated with improvement over placebo, the magnitude of the HDL-C benefit differed considerably. CEE alone was associated with the greatest increase, followed by CEE plus MP. The difference between those 2 groups was small and statistically insignificant. The improvements in the 2 MPA arms were better than placebo, but the benefits were only about one third of that associated with administration of CEE alone or CEE plus MP.

PEPI, therefore, demonstrated that MP had a minimal and nonsignificant attenuating effect on the CEE-associated improvement in HDL-C, while MPA in both continuous and cyclical regimens significantly attenuated this estrogen benefit.¹

Another clinical trial evaluated the effects of 17 β -estradiol combined with either NETA or norgestimate on lipid measures. Again, effects on HDL-C differed considerably: Whereas NETA was associated with a 12.3% reduction, norgestimate administration provided a 4.8% increase in HDL-C. The effects of progestogens on HDL-C preservation is shown in **FIGURE 3**. Both regimens provided significant decreases in LDL-C (17.9% and 14.9%, respectively).¹²

Dr Simon noted in his introduction that head-to-head trials seldom address the potency of various progestogens. The effects of these progestogens on HDL-C shed some light in this area: NETA is associated with relatively strong attenuation of estrogen effects. MPA is moderately attenuating; norgestimate and MP are progressively less attenuating. Of all available progestogens, MP has the smallest effect in reducing estrogen's benefits (**FIGURE 3**).¹³⁻¹⁵

Hormone therapy and glucose metabolism

Insulin resistance, which clinically is assessed most often through glucose metabolism, is an important cardiovascular risk factor in women. In 2-hour glucose tolerance tests conducted in the PEPI study, women who received CEE/MP or CEE alone had insulin metabolism that, statistically, was insignificantly different from that of women who received placebo. However, both MPA regimens showed a significant worsening in this measure, specifically increases in insulin resistance of 7% to 7.5%

that could be associated with a meaningful increase in cardiovascular risk.^{1,16}

Data from PEPI were analyzed further to project the 10-year CHD risk associated with the lipid and carbohydrate effects of PEPI regimens in a population aged 45 to 64 years. Using the Framingham risk equation for lipids and blood pressure and the World Health Organization estimates for glucose metabolism, PEPI data suggest that CEE/MPA regimens could reduce 10-year CHD risk by 6%; CEE/MP by 19%; and CEE alone by 23%.¹⁷ While the PEPI publications compared the treatments for each factor and found no statistical difference for CEE alone and CEE plus MP in post-challenge glucose, the risk calculation incorporated the achieved levels of glucose, HDL, LDL, and blood pressure simultaneously.^{16,18}

Coronary effects of estrogens/progestogens: Primate studies

A series of studies on primates with an estrous cycle and metabolic profile very similar to humans have shed light on tissue-level effects of HT in the coronary arteries. Williams et al evaluated the effect of HT on acetylcholine-induced vasospasm in the coronary arteries of surgically postmenopausal monkeys.¹⁹ They showed that estradiol-treated monkeys were protected against the vasospasm that occurred in the untreated animals.

Other investigators examined the effects of estrogen plus progestogens in the same model. In a 4-week study, physiologic levels of 17 β -estradiol and either MPA or progesterone were administered to mimic the effects of HT in humans.²⁰ Monkeys treated with estradiol plus MPA consistently demonstrated vasospasm when challenged with acetylcholine, a response equivalent to untreated animals. In contrast, coronary blood flow remained intact in the monkeys treated with estradiol plus progesterone, a response equivalent to what was seen with estradiol alone. This study demonstrated that MPA and progesterone have distinctly different effects on acute blood flow in coronary arteries; the estrogen effect is preserved with progesterone but ablated by MPA.

Additional primate studies assessed the development of atherosclerotic plaque and the potential effects of estrogen and progestogens on the development of cardiovascular disease. These findings are of particular relevance when assessing the results of the WHI, in which most participants were 12 years postmenopausal and in whom cardiovascular disease had already developed.

The ovariectomized monkeys in these studies were fed a high-fat chow for 2 years to mimic the atherogenic diet prevalent in our society. They were then treated with equivalent doses for weight of typical HT regimens for 30 months. The end point was the degree of luminal atheroma present at specific anatomic locations in the coronaries. Both CEE and estradiol protected against atheroma in placebo-controlled trials. However, when MPA was added to the CEE, protection against atheroma was lost. In contrast, progesterone plus estradiol provided a reduction in atheroma equivalent to estradiol alone. MPA therefore blocked the long-term effect of estrogen in the coronary arteries while progesterone did not attenuate the benefits of estrogen (FIGURE 4).^{21,22}

Progestogens and quality of life

A study by Fitzpatrick et al²³ assessed these effects in 176 women who had taken estrogen plus MPA for an average of 5 years and presented with quality-of-life concerns potentially related to that regimen. These women completed a standardized questionnaire and then were switched to a regimen that used MP. After 6 months on the MP regimen, the standard survey was repeated.

The assessment included the Greene Climacteric scale (21 items regarding vasomotor, somatic, and psychological symptoms) and the 36-question Women's Health Questionnaire (WHQ), which assessed a variety of somatic symptoms, mood/anxiety symptoms, and cognitive and sexual functioning.

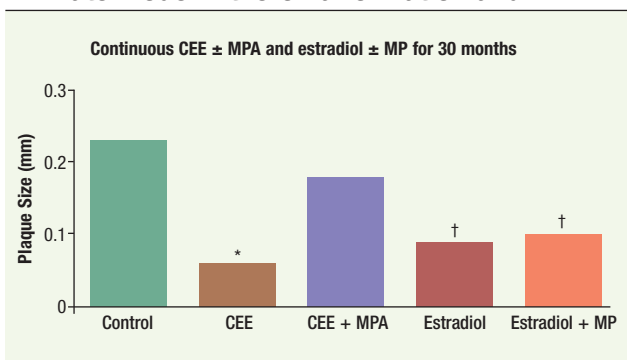
Highly significant improvements ($P < .001$) were achieved for all subscales, except for the sexual attraction component of the WHQ. The difference in bleeding and symptom control accounted for majority of the greater satisfaction with MP. The study illustrates that for women who have experienced difficulty with MPA, MP may offer a preferable alternative (FIGURE 5).²³

Progestogens and the breast

The relative effects of common HT regimens on mammographic density were evaluated in the PEPi trial. Changes in breast density for yearly intervals were assessed using Bi-Rads scores assessed by a reader unaware of treatment assignment from digitized annual mammograms. Relatively few women had any annual change. Of those who did, women assigned to CEE alone had the least increase in density, followed by

FIGURE 4

Primate model: Atheroma formation and HT



CEE, conjugated equine estrogen; HT, hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone.

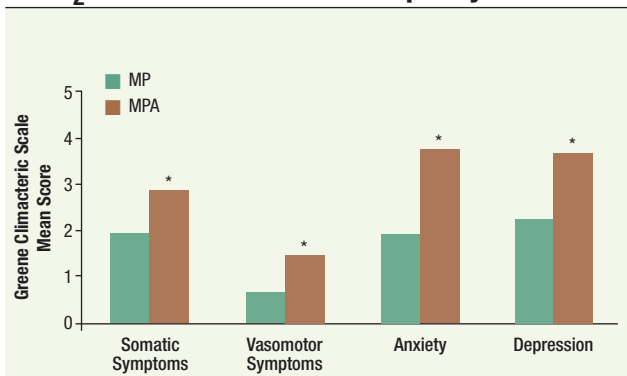
* $P < .05$ versus all groups.

† $P < .05$ versus control.

Adams MR, et al. *Arterioscler Thromb Vasc Biol.* 1997;17:217-221. Adams MR, et al. *Arteriosclerosis.* 1990;10:1051-1057.

FIGURE 5

HT: E₂ + MPA or MP: Effect on quality of life



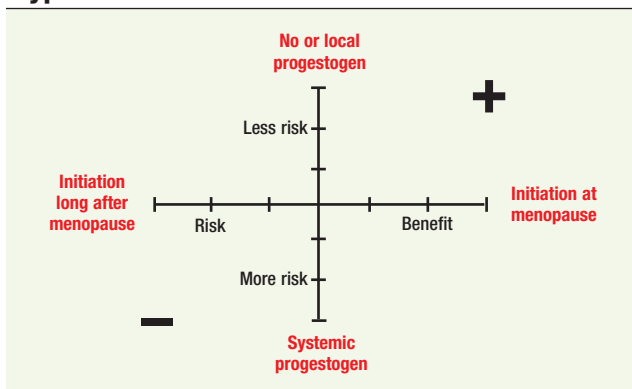
E₂, estradiol; HT, hormone therapy; MP, micronized progesterone; MPA, medroxyprogesterone.

* $P < .001$ versus MP.

Fitzpatrick LA, et al. *J Womens Health Gen Based Med.* 2000;9:381-387.

women assigned to CEE plus cyclical MP, then CEE plus cyclical MPA. Women assigned to CEE plus continuous MPA were the most likely to demonstrate an increase in breast density.²⁴ These results are consistent with findings from primate studies that demonstrate an increase in mammary epithelial and terminal duct proliferation in animals treated with CEE plus MPA, compared to those given CEE alone.²⁵ In the WHI trial of continuous CEE plus MPA, the rate of abnormal mammograms was about 10% higher in women assigned to active treatment compared to placebo beginning with the first annual assessment. This group also had an excess rate of breast cancer (hazard ratio [HR] 1.24, $P < .001$) that was evident after the third year.²⁶ Given

FIGURE 6
Hypothesis: CHD benefit and risk with HT



CHD, coronary heart disease; HT, hormone therapy.
 Philips LS, Langer RD. *Fertil Steril.* 2005;83:558-566.

the unexpectedly short time for the breast cancer difference to become evident, an effect on initiation is uncertain. The increased surveillance of treated women generated by the breast density increase cannot be excluded as an explanation for this difference. In contrast, in the WHI trial of CEE alone, there was no increase in breast cancer among women assigned to active treatment. In fact, there was a nonsignificant lower rate of breast cancer with CEE in the absence of a progestogen (HR .82, $P = .10$).²⁷

A nonintervention study with an average of about 3 years of exposure found an insignificant increase in breast cancer in women taking estrogen alone (relative risk [RR] 1.1, 95% confidence interval [CI] .8-1.6), a significant increase for HT with synthetic progestins (RR 1.3, CI 1.1-1.5), but no increase in women taking HT with MP (RR .9, CI .7-1.2). That study, which was conducted in Europe, provides an interesting contrast because the majority of estrogen use was transdermal estradiol.²⁸ It is possible that the specific estrogens used, and the route of administration, could also be important in assessing breast cancer risk.

In summary, the presence and potency of the progestogen influences breast density, the frequency of abnormal mammograms, and the rate of breast cancer detection.

New progestins and their potential applications

Although the review presented so far in this article has only included agents assessed by long-term studies, new options are emerging. Drospirenone, a derivative of

17-spironolactone, was recently approved for use in HT. The bioactivity profile of drospirenone is similar to that of natural progesterone, and it has been used in an oral contraceptive available in the United States since 2001. This novel progestin has anti-aldosterone and anti-androgenic properties and, as a result, may reduce some side effects associated with estrogen, such as fluid retention.

Drospirenone protects against endometrial hyperplasia, and it is associated with a modest degree of bleeding, a low rate of breast discomfort, and lipid effects comparable to those of other HT formulations. A decline in triglycerides and reduction in blood pressure of approximately 9 mm Hg is also seen with this agent.²⁹

The levonorgestrel intrauterine device also provides endometrial protection when used in conjunction with estrogen for HT. Although this use is not approved in the United States, it is licensed in many other countries. The device produces minimal or no systemic progestogen effect. In a study comparing the 2 dosage ranges of the intrauterine device with sequential oral MPA, the intrauterine devices provided effective protection against endometrial disease.³⁰

Conclusion

HT-associated cardiovascular benefits and risks may be evaluated using a matrix that accounts for the effects of years since menopause (subclinical disease) and the potency of the progestogen (degree of attenuation to the estrogen effect) (FIGURE 6).³¹ Based on available data, initiation of estrogen therapy long after menopause results in no effect (as demonstrated by the overall results of the WHI estrogen-alone trial), whereas initiation at menopause is protective, as shown by the age-specific results of the WHI estrogen study.

The use of a potent systemic progestogen carries increased cardiovascular risk that is particularly evident in women 10 or more years postmenopausal (as shown by the WHI CEE-plus-MPA trial), whereas a locally or minimally attenuating progestogen may preserve an estrogen benefit.

HT, administered at the time of menopause, does appear to offer benefits, in contrast to the overall data reported by the WHI. Timing of initiation is critical for cardiovascular effects. Starting within 10 years of menopause is likely to have beneficial effects on coronary disease; starting later than that may be associated with increased coronary risk, at least for the first few years.

The potency and route of administration of the progestogen also deserve consideration because the choice of a progestogen can have significant effects in preserving or attenuating the benefits that may result from estrogen administration. Clinicians should consider carefully the relative merits of an HT regimen based on characteristics of the individual woman, and the treatment goals.

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Essential Areas and Policies. Credit is available through February 2009. The estimated time to complete this activity is 2 hours.

Read through the activity beginning on page 3 and select the best answer for each of the following questions. The test form and mailing instructions are on the next page.

- 1. Progesterone and progestins differ in terms of which of the following?**
 - A. Cardiovascular effects
 - B. Androgenic effects
 - C. Antimineralocorticoid effects
 - D. All of the above
- 2. The incidence of secondary amenorrhea is highest in women aged**
 - A. 15 to 24 years
 - B. 25 to 30 years
 - C. 31 to 36 years
 - D. 37 to 44 years
- 3. A study by Shangold identified the dosage of progesterone above which bleeding is always induced.**
 - A. True
 - B. False
- 4. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial reported whthe following effects on high-density lipoprotein cholesterol associated with hormone therapy (HT)**
 - A. All progestogens attenuate estrogen's benefits
 - B. Continuous medroxyprogesterone acetate (MPA) preserves estrogen's benefits
 - C. Micronized progesterone preserves estrogen's benefits
 - D. Cyclical MPA preserves estrogen's benefits
- 5. Women are likely to decide to discontinue or reject HT because of**
 - A. Breakthrough bleeding or spotting
 - B. Concerns about breast cancer
 - C. Treatment side effects
 - D. All of the above
- 6. Women enrolled in the Women's Health Initiative (WHI) were**
 - A. Representative of women who use HT
 - B. Recruited for the severity of menopausal symptoms
 - C. Characterized by preexisting cardiovascular disease
 - D. Significantly older than the typical woman who would use HT for relief of menopausal symptoms
- 7. Women who were aged 50 to 59 years at the start of the WHI study and received estrogen-only HT had a 34% reduction in total coronary events.**
 - A. True
 - B. False
- 8. Luteal-phase defect may be present in women with regular menstrual cycles.**
 - A. True
 - B. False
- 9. In women aged 60 to 79 years, estrogen-only HT has been found to be**
 - A. Neither beneficial nor harmful in coronary outcomes
 - B. Harmful in coronary outcomes
 - C. Beneficial in coronary outcomes
- 10. Vasomotor symptoms may be a useful marker of estrogen deficiency and, therefore, an indicator of women who may benefit from HT.**
 - A. True
 - B. False

CME Posttest Answer Sheet / Evaluation Form

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Record your answers here by circling the appropriate letter:

- | | | | |
|------------|------------|----------|---------|
| 1. A B C D | 4. A B C D | 7. A B | 10. A B |
| 2. A B C D | 5. A B C D | 8. A B | |
| 3. A B | 6. A B C D | 9. A B C | |

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| NAME (FIRST) | (LAST) | (DEGREE) |
| STREET ADDRESS | | |
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The activity objectives and needs assessments were fully met.

Strongly agree Agree Disagree Strongly disagree

COMMENTS:

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COMMENTS:

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■ **Communicate with patients**

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