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Progesterone: Review of Safety for Clinical Studies

Nathalie V. Goletiani
Harvard Medical School and McLean Hospital

Diana R. Keith and Sara J. Gorsky
McLean Hospital

Progesterone is a steroid hormone that is important for reproductive function. Progesterone is used in a number of clinical applications and has been investigated as a possible novel approach for treatment of stimulant drug abuse. Extensive clinical studies have been conducted to examine the subjective and physiological effects of exogenous progesterone administration and to evaluate its side effects. This review summarizes the safety and side effects of acute and chronic administration of 3 progesterone formulations (synthetic, natural, and micronized natural), several routes of administration (oral, intramuscular, intravenous, intravaginal, intranasal, transdermal, and rectal), and dosing regimens. Synthetic progestins marketed as Provera, PremPro, and Cycrin are widely used but may produce a number of significant side effects, such as fatigue, fluid retention, lipid level alterations, dysphoria, hypercoagulant states, and increased androgenicity. Natural progesterones are reported to have milder adverse effects, depending on the route of administration. Micronized natural progesterone is available for oral administration, has better bioavailability and fewer side effects than natural progesterone, and is convenient to administer. Therefore, micronized natural progesterone appears to be a safe and effective alternative to synthetic and natural progesterone formulations for variety of clinical and research applications.

Keywords: progesterone, micronized progesterone, synthetic progesterone

Progesterone is a steroid hormone produced in both men and women by the adrenal cortex and gonads, in the central and peripheral nervous systems (CNS and PNS), and in women by the placenta during pregnancy (Lo & Lamb, 2004; Rhen & Cidlowski, 2004; Strauss, 2004; Yen, 2004). Progesterone is synthesized from pregnenolone, a derivative of cholesterol (Schumacher et al., 2007; Strauss, 2004). In progesterone biosynthesis, cholesterol is converted through the enzymatic action of cytochrome P450 to pregnenolone, which is then converted to progesterone by 3-beta-hydroxysteroid dehydrogenase/Δ5, Δ4 isomerase in the smooth endoplasmic reticulum. From this point, progesterone may enter a variety of biochemical pathways to synthesize various steroid hormones. Two major enzymes are involved in further metabolism of progesterone: 5 alpha reductase-I/II and 5 beta reductase, producing 5 alpha dihydroprogesterone and 5 beta dihydroprogesterone, respectively. This is the rate-limiting step in the metabolism of progesterone. The first pathway, via 3 alpha hydroxysteroid dehydrogenase (HSD)-II/III enzyme, results in production of 3 alpha 5 alpha-tetrahydroprogesterone (THP; allopregnanolone), the main neuroactive steroid, and 3 alpha 5 beta-THP (isoallopregnanolone). The second pathway produces 3 alpha 5 beta-THP (pregnanolone) via 3 alpha HSD and 3 beta 5 beta-THP (isopregnanolone) via 3 beta HSD enzymes (Finn et al., 2006; Niswender, 2002; Pluchino et al., 2006; Schumacher et al., 2007).

Allopregnanolone is a potent modulator of GABA-A receptor activity, but its 3 beta epimer, isoallopregnanolone, is inactive on GABA-A receptors and has been shown to antagonize the effects of allopregnanolone (Backstrom, Wahlstrom, Wahlstrom, Zhu, & Wang, 2005; Lundgren, Stromberg, Backstrom, & Wang, 2003; Schumacher et al., 2007). Some of the neuromodulatory and protective effects of allopregnanolone may contribute to the benefit and side effects of progesterone administration. Specifically, allopregnanolone has been shown to produce anticonvulsant, antidepressant, anxiolytic, and neuroprotective effects in experimental animals as well as in tissues and cell cultures (Finn et al., 2006; Schumacher et al., 2007; M. Singh, 2005). Human data are more complicated, and several studies have been conducted in an effort to evaluate the neuromodulatory effects of progesterone and its metabolites. For example, allopregnanolone has been found to be dose-dependently involved in the pathogenesis of premenstrual syndrome (PMS), premenstrual dysphoric disorder (Andreen et al., 2005; Girdler, Straneva, Light, Pedersen, & Morrow, 2001; N-Wihlbäck, Sundström-Poromaa, & Bäckström, 2006; Wang, Seippel, Purdy, & Backstrom, 1996), and major depression (Uzunova et al., 1998) and to exhibit negative sedative effects, such as fatigue, confusion, and delayed verbal recall and symbol copying (Freeman, Purdy, Coutifaris, Rickels, & Paul, 1993). Decreased biosynthesis

Nathalie V. Goletiani, Alcohol and Drug Abuse Research Center, Harvard Medical School and McLean Hospital; Diana R. Keith and Sara J. Gorsky, McLean Hospital, Belmont, Massachusetts.

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Correspondence concerning this article should be addressed to Nathalie V. Goletiani, Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02478. E-mail: ngoletiani@mclean.harvard.edu

of allopregnanolone also appears to contribute to the severity of withdrawal in individuals with alcoholism (Romeo et al., 1996).

Progesterone can further be converted to a variety of steroid hormones and is a precursor of the mineralocorticoid aldosterone, the glucocorticoid cortisol, and the sex steroid androstenedione (Strauss, 2004). Androstenedione can, in turn, be converted to testosterone, estrogen, and estradiol.

An inhibitor of progesterone metabolism, finasteride, prevents the conversion of progesterone to allopregnanolone. This inhibitor has been shown to reduce the subjective responses to alcohol in clinical studies (Finn et al., 2006; Pierucci-Lagha et al., 2005).

Progesterone acts primarily via intracellular progesterone receptors. Although the progesterone receptor is expressed by a single gene on chromosome 11q22, it is represented by two main isoforms, A and B, that differ in molecular weight (Rhen & Cidlowski, 2004). These isoforms may occur in different cells, and the A form is more prevalent (Rhen & Cidlowski, 2004; Vegeto et al., 1993).

Progesterone receptors are present in abundance throughout the body and are specifically found in the brain (hypothalamus and pituitary) of primates and humans (Luetjens et al., 2006), the thymus (Ishibashi et al., 2003), the cardiovascular system (aortic PR-A isoform more prevalent in women than in men; Nakamura et al., 2005), the mammary gland of primates and humans (Luetjens et al., 2006; Russo, Ao, Grill, & Russo, 1999), the reproductive tract (in uterus, cervix, vagina, ovaries) in women (Christow, Sun, & Gemzell-Danielsson, 2002), and in the testes, prostate, and seminal vesicles of primates and men (Luetjens et al., 2006; Williams et al., 2001). Progesterone receptors are also present in bones (MacNamara, O'Shaughnessy, Manduca, & Loughrey, 1995; Tremollieres, Strong, Baylink, & Mohan, 1992), the pancreas (Friess, Buchler, Kiesel, Kruger, & Beger, 1991), the gastrointestinal tract (Franz, Wendler, & Oettling, 1996; Meggouh, Lointier, Pezet, & Saez, 1991; Meggouh, Lointier, & Saez, 1991; Oettling & Franz, 1998; S. Singh, Sheppard, & Langman, 1993; Xiao, Pricolo, Biancani, & Behar, 2005), and the bladder and urethra (Blakeman, Hilton, & Bulmer, 2000; Celayir, Ilce, & Dervisoglu, 2002). Thus, it appears that progesterone plays an important role in the regulation of many body functions in addition to reproduction. Progesterone and its neuroactive metabolites, such as allopregnanolone, are also involved in modulation of sleep (Soderpalm, Lindsey, Purdy, Hauger, & de Wit, 2004), memory, and gonadotropin secretion and have neuroprotective abilities, such as facilitating myelinization in both the CNS and PNS (Backstrom et al., 2005). They also have effects on sexual behavior and respiratory function, control appetite and weight gain, modulate tumorigenesis in the CNS, and are involved in the pathogenesis of affective disorders and epilepsy (Oettel & Mukhopadhyay, 2004).

In men, progesterone is involved in spermiogenesis, sperm capacitation–acrosome reaction, and androgen biosynthesis in Leydig cells (Oettel & Mukhopadhyay, 2004). In women, progesterone is commonly referred to as a "hormone of pregnancy" because it plays a vital role in preparing the endometrium for implantation, successful gestation, and normal development of the fetus (Carmina & Lobo, 2004; Mesiano & Jaffe, 2004). Progesterone is also essential for preventing lactation during pregnancy. Decreasing levels of progesterone initiates the withdrawal bleeding that marks the onset of menstruation (Hall, 2004; Strauss & Williams, 2004).

In women, progesterone levels are relatively low (< 2 ng/ml) during the follicular phase of the menstrual cycle. However, progesterone production in the follicular phase is required for ovulation and is mediated by luteinizing hormone (LH) as one of its early actions in the ovulatory process. Induction of progesterone receptors in ovarian granulosa cells occurs within hours of pulsatile LH release (LH surge) during ovulation (Strauss & Williams, 2004). This was demonstrated by studies using progesterone receptor antagonists and progesterone synthesis inhibitors to prevent ovulation in rats (DePaolo, 1988; Gaytan, Bellido, Gaytan, Morales, & Sanchez-Criado, 2003; Micevych et al., 2003) and monkeys (Hibbert, Stouffer, Wolf, & Zelinski-Wooten, 1996; Remohi, Balmaceda, Rojas, & Asch, 1988). After ovulation occurs, the ruptured follicle is reorganized into the corpus luteum, which produces increasing amounts of progesterone during the luteal phase. Progesterone reaches its maximal levels (> 5 ng/ml) in the midluteal phase of the cycle (Carmina & Lobo, 2004; Strauss, 2004). In men, progesterone levels are low and are similar to levels observed in women in follicular phase of the menstrual cycle (Lo & Lamb, 2004).

Clinical Applications

Progesterone, usually in combination with estrogen, is most commonly used clinically for contraception and to treat women with secondary amenorrhea, dysfunctional vaginal bleeding, and endometrial hyperplasia in hormone replacement therapy (HRT; de Lignieres, 1999; Lobo, 2004). Progesterone also has some additional clinical applications, as a treatment for hypertension, stimulant drug dependence, chronic obstructive pulmonary disease (Bales & Timpe, 2004; Wagenaar, Vos, Heijdra, Teppema, & Folgering, 2003), and benzodiazepine withdrawal (Evans & Foltin, 2006; Moran, Goldberg, & Smith, 1998; Schweizer, Case, Garcia-Espana, Greenblatt, & Rickels, 1995; Simon et al., 1993; Sofuoglu, Babb, & Hatsukami, 2002; Sofuoglu, Mitchell, & Kosten, 2004). Chronic progesterone administration may have a number of side effects, including abdominal cramps, back pain, breast tenderness, constipation, nausea, dizziness, edema, vaginal bleeding, hypotension, fatigue, and dysphoria and may induce a hypercoagulant state (Physicians' Desk Reference, 2006). Progesterone has been administered to both men and women in clinical studies (de Lignieres & Vincens, 1982; Dennerstein et al., 1985; de Wit, Schmitt, Purdy, & Hauger, 2001; Evans & Foltin, 2006; Freeman, Weinstock, Rickels, Sondheimer, & Coutifaris, 1992; Gron, Friess, Herpers, & Rupprecht, 1997; Little, Matta, & Zahn, 1974; Rylance et al., 1985; Shangold et al., 1991; Simon et al., 1993; Soderpalm et al., 2004; Sofuoglu, Babb, & Hatsukami, 2002; Sofuoglu et al., 2004; Tollan, Oian, Kjeldsen, Eide, & Maltau, 1993).

Recently, progesterone has been investigated as a possible novel approach to the treatment of drug abuse–depen-

dence on stimulants, such as cocaine and nicotine. Natural fluctuations in progesterone across the menstrual cycle appeared to affect subjective responses to cocaine (Evans, Haney, & Foltin, 2002). During the luteal phase, when progesterone levels were high, ratings of positive subjective effects of cocaine were lower than during the follicular phase, when progesterone levels were low (Evans et al., 2002). Chronic (150 mg once a day for 3 days) exogenous progesterone administration attenuated the positive subjective effects of smoked cocaine in women in the follicular phase of their menstrual cycle, but only minimal changes in subjective effects ratings were detected in men (Evans & Foltin, 2006). However, acute progesterone treatment diminished the physiological and subjective effects of intravenous cocaine in both male and female cocaine users (Sofuoglu et al., 2004). Similarly, after a single 200-mg po dose of progesterone, the average of a Cocaine Effects Questionnaire (CEQ) was attenuated in female cocaine smokers (Sofuoglu et al., 2002). In female cigarette smokers, attenuation of craving and subjective effects of nicotine were observed during progesterone treatment in the early follicular phase of the menstrual cycle, and there was a trend for smoking behavior to decrease after a single 200-mg po progesterone administration (Sofuoglu et al., 2001). Finally, phencyclidine self-administration was decreased during the follicular phase compared with the luteal phase of the menstrual cycle in rhesus monkeys (Newman, Thorne, Batulis, & Carroll, 2006). Progesterone administration also dose-dependently decreased cocaine self-administration by female rhesus monkeys (Mello, Knudson, Kelly, & Mendelson, 2007).

Formulations

Currently, progesterone is available in several formulations, including natural progesterone, micronized natural progesterone, and synthetic progestins. Natural progesterones, analogs of ovarian progesterone, can be administered through different routes and have different absorption rates. Synthetic progestins are not chemically identical to progesterone and can cause undesirable side effects (Simon et al., 1993). Micronized natural progesterone was developed in the late 1970s and was available for clinical use in the early 1980s. Micronization of natural progesterone decreases the size of the progesterone particle (Morville, Dray, Reynier, & Barrat, 1982), which increases the surface area of the steroid to facilitate absorption and results in an exponential increase in the bioavailability of micronized natural progesterone compared with the natural nonmicronized form. Micronized natural progesterone is chemically identical to ovarian progesterone and is synthesized from a precursor extracted from Mexican yams, soybeans, and, sometimes, animal sources (Apgar & Greenberg, 2000; de Lignieres, 1999). Micronized natural progesterone is effective for various clinical applications, such as secondary amenorrhea, HRT, endometrial hyperplasia, and dysfunctional bleeding. The micronized form was shown to have significantly fewer metabolic and vascular side effects than the synthetic progestins (please see de Lignieres, 1999, for discussion). Examples of some currently available preparations are described in each section below. Illustrative studies that have assessed the safety of these three progesterone formulations in relation to the route of administration are reviewed in the remainder of this article. Although progesterone–estradiol treatments are briefly discussed, the sections below focus on studies that use progesterone-only treatments to elucidate the progesterone-specific side effects and its safety and tolerability.

Synthetic Progestins

Synthetic progestins have a number of applications in clinical medicine. They are commonly used for birth control as oral and long-acting contraceptives in premenopausal women, as HRT in postmenopausal women, and to treat dysmenorrhea uterine bleeding; hypogonadism; polycystic ovary disease; endometriosis; breast, kidney, or endometrial cancer; cancer–AIDS-related anorexia or weight loss; and acne (Apgar & Greenberg, 2000; Henzl, 2001; Schacter et al., 1989; Unfer et al., 2005). Although synthetic progestins are typically well tolerated, they are contraindicated in patients with thrombophlebitis, thromboembolic disorders, cerebral vascular disease, coronary artery disease, known or suspected pregnancy, or breast cancer and in smokers (especially over the age of 35) as well as those with impaired liver function (Physicians' Desk Reference, 2006).

Synthetic progestins were traditionally the preferred formulation for progesterone treatment before the development of micronized natural progesterone because they are inexpensive and easy to produce. Synthetic progestins were also originally designed to overcome the poor absorption of oral preparations of natural progesterone. Synthetic progestins are less susceptible to enzymatic degradation but virtually duplicate the activity of natural progesterone in the uterus. However, because synthetic progestins are not chemically identical to natural progesterone, some progestins exert androgenic effects in the CNS and may also produce alterations in lipid levels (decreased high-density lipoprotein in postmenopausal women), glucose metabolism, vasomotility, dizziness, and sedation (de Lignieres, 1999; Little et al., 1974).

Synthetic progestins are currently available as a progesterone preparation or in combination with estrogen. Progestin-only preparations are typically used when there are contraindications to estrogen, such as in breast-feeding mothers and older women (Rosen & Cedars, 2007). Synthetic progestins can be administered in oral form and in long-acting preparations, such as subdermal implants, in intrauterine devices (IUD), and parenterally. Synthetic progestins administered orally for contraception as progestin-only pills include norethindrone as an active ingredient (Noriday, Aygestin, Nor-QD, Nora-Be, etc.), medroxyprogesterone acetate (MPA; Provera, Cycrin, Amen), and levonorgestrel (LNG; Plan-B; Physicians' Desk Reference, 2006). In addition, LNG (Norplant-system, Jadelle, Implanon) used for contraception can also be implanted subdermally (Physicians' Desk Reference, 2006). Furthermore, 17-a-hydroxyprogesterone caproate (Delalutin) and MPA (medroxyprogesterone acetate–Depo-Provera) are used parenterally and LNG (Mirena) is an active ingredient in the

intrauterine contraceptive device (Physicians' Desk Reference, 2006). Noncontraceptive progestin-only products prescribed for abnormal uterine bleeding, amenorrhea, and uterine preparation for menses include hydroxyprogesterone (Gesterol LA 250, Hy/Gestrone, Hylutin/Prodrox, and Pro-Span) parenterally and medroxyprogesterone administered orally (Provera), which can also be used as part of menopausal HRT with estrogen (Fraser & Kovacs, 2003). The latter, administered intramuscularly (Amen, Curretab, Depo-Provera), is commonly prescribed for kidney, prostrate, breast, ovarian, and endometiral cancer (Robustelli della Cuna et al., 1986). Another synthetic progestin, megestrol (Megace), is prescribed in oral and liquid form for treatment of breast or uterine cancer and for appetite induction for weight loss related to cancer and AIDS (Schacter et al., 1989). Finally, oral norethindrone (Aygestin) in a tablet form is prescribed for abnormal uterine bleeding, amenorrhea, or endometriosis ("Norethisterone and Norethisterone Acetate," 1979).

Progestins are conventionally classified as two groups, new and old progestins, which, in turn, are divided into three generations depending on derivative (Sitruk-Ware, 2006). For example, norethynodrel and nortestosterone are considered to be first generation and are activated after conversion to noresthisterone (Estranes). Gonanes, such as norgestrel and LNG, belong to the second generation of progestins. The LNG derivatives, such as desoestrel (DSG), etonogestrel (DSG derivative in Implanon and NuvaRing), gestodene, norgestimate, and norelgestromine (norgestimate derivative in Evra), are classified as the third generation of progestins. The majority of progestins in all three generations are testosterone-derived and therefore exhibit undesirable androgenic effects because, despite modification, they still bind to the androgen receptor (AR). Others that are derived from progesterone (17 hydroxyprogesterone derivatives), hydroxyprogesterone (19 norprogesterone derivatives), or spironolactone (drospirenone) have been found to exert estrogenic, glucocorticoid, and mineralocorticoid actions (Pluchino et al., 2006). New progestins include drospirenone, dienogest, trimegestone, Nestorone (NES), and nomegestrol acetate (NOMAc). New generation progestins were synthesized to bind exclusively to the progesterone receptor (PR) to avoid androgenic, estrogenic, mineralocorticoid, and glucocorticoid adverse effects (Kuhl, 1996; Schindler et al., 2003; Stanczyk, 2002).

Combined Synthetic Progestin–Estradiol Preparations

Synthetic progestins in combination with ethinyl estradiol are administered orally for contraception and include norethindrone acetate (Brevicon, Leena, Low-Ogestrel, Necon, Norinyl) and LNG (Levore, Lutera, Trivora; Physicians' Desk Reference, 2006). Synthetic progestins administered orally for HRT are combinations of norethindrone acetate with ethinyl estradiol (Activella) and medroxyprogesterone with conjugated estrogens (Premphase, Prempro; Koubovec, Ronacher, Stubsrud, Louw, & Hapgood, 2005). Transdermal norethindrone acetate–estradiol combination preparations (CombiPatch) are also used for HRT, and norelgestromin–ethinyl estradiol combination preparations (Ortho Evra patch) are used for birth control (Henzl & Loomba, 2003). Another combination preparation of etonogestrel–ethinyl estradiol (NuvaRing) is administered intravaginally for contraception (Szarewski, 2002).

Oral Administration of Synthetic Progestins

Studies in women. Synthetic progestins have been extensively studied in premenopausal and postmenopausal women, and the time course of plasma–serum levels of progestins has been measured. In one study, the effects of NOMAc on circulating hormone levels, metabolic and hemostatic parameters, and blood pressure were examined. After chronic oral administration of 5 mg NOMAc to 36 premenopausal women from Days 7 to 25 during each of six cycles, a serum level of 8 ng/ml was detected within 4 hr. This dose of NOMAc did not affect the serum levels of sex hormone binding globulin (SHBG), corticosteroid binding protein (CBG), angiotensinogen, GHL cholesterol, low-density lipoprotein cholesterol, fibrinogen, or plasminogen but did increase antithrombin and reduce triglycerides (Basdevant et al., 1991). In another study, the pharmacokinetics of norethisterone acetate (NETA) administered alone or in combination with estradiol was examined in 24 postmenopausal women in a randomized crossover trial. These subjects were given a single oral dose of NETA (0.5 mg), administered alone or in combination with estradiol (E2; 1 mg). An acute dose of 0.5 mg NETA produced peak concentrations of 19.3 nmol/l within 0.75 hr. The same dose of 0.5 mg NETA, in combination with 1 mg E2, was also administered chronically in daily doses for 28 days. This combination produced no change in the bioavailability of progesterone. There were no adverse events during the study, and no side effects were reported (Stadberg et al., 1999). The pharmacology, clinical applications, and safety of the synthetic progestins, natural progesterone, and micronized natural progesterone were compared in a review by de Lignieres (1999). Commonly reported side effects, such as dizziness and sedation, have been documented after administration of oral synthetic progestins (Little et al., 1974). In clinical practice, the adverse impact of these side effects can be avoided by administering the drug at bedtime (de Lignieres & Vincens, 1982).

Studies in men. To compare the bioavailability of a micronized megestrol acetate tablet formulation with a conventional oral form, 24 male subjects received an acute oral administration of 160 mg megestrol acetate or micronized megestrol acetate (Farinha, Bica, & Tavares, 2000). Plasma progesterone Cmax mean values reached 125 ng/ml in the micronized form and 45 ng/ml in the conventional synthetic progestin form. Both formulations had Tmax mean values of 6.3 and 8.0 hr, respectively. A significant increase in bioavailability of micronized synthetic progestins versus the conventional form was documented. No side effects or adverse reactions were reported, and no serious side effects were observed after doses up to 800 mg (Gaver et al., 1985).

The subjective and physiological effects of exogenous progesterone administration were investigated in one of the first double-blind placebo-controlled studies (Little et al.,

1974). An oral synthetic progestin, Provera (10 mg/day), was given to 6 men for 1 week during a 4-week period of testing. Identical placebo pills were given for the other 3 weeks. These placebo and progesterone treatments were given in a random order under double-blind conditions. The purpose of this clinical study was to examine the physiological and psychological effects of progesterone administration. Measures of skin conductance, heart rate, temperature, and respiration as well as mood tests, time estimation, and reaction rates were recorded on 4 days each week throughout the 4-week period. However, serum concentrations of progesterone were not measured. Progesterone administration lowered skin conductance levels, raised temperature, and decreased heart rate variability. It also increased reports of "sluggishness," even up to a week after progesterone administration was discontinued. However, no significant adverse effects were reported after daily progesterone administration to healthy men (Little et al., 1974).

Nonoral Administration of Synthetic Progestins

Nonoral preparations of synthetic progestins are particularly useful because they avoid the first-pass effect of steroidal hormones on the liver (Sitruk-Ware, 2007b). Nonoral long-acting preparations have also become increasingly popular because of the rise in unplanned pregnancies in noncompliant users of oral contraceptives because these methods of contraception offer convenience and ensure contraceptive compliance. Sustained hormone release regimens augment the effectiveness of these long-acting preparations, and the lowest therapeutic dose can be used for target organ delivery, thereby avoiding high circulating levels and potential deleterious effects on the heart and breasts while remaining beneficial for noncontraceptive purposes, such endometrial cancer therapy (Rosen & Cedars, 2007; Sitruk-Ware, 2007b).

Long-Acting Synthetic Progestin-Only Preparations

Long-acting progestin-only preparations include subdermal implants; transdermal patches, gels, and sprays (currently in development); IUDs; and injectables (parenterally).

Subdermal Administration of Synthetic Progestins

Several subdermal progestin-only implants have been developed and contain four different progestins (Meirik, Fraser, & d'Arcangues, 2003). Some of these systems are outdated and have been taken off the market since new, more convenient and easier to use systems have become available. Others are still in development (Croxatto, 2002b). Subdermal progestin-only contraceptives include LNG implants (Norplant, Norplant II, and Jadelle), etonogestrel-releasing implants (Implanon), NES 16-methylene-17alpha-acetoxy-19-norpregn-4-ene-3, 20-dione-containing implants (NES, ST-1435 silicon rod and Elcometrine silicone capsule), and NOMAc implants (Uniplant; Croxatto, 2002a, 2002b; Meirik et al., 2003; Zheng, Zheng, Qian, Sang, & Kaper, 1999). Contraceptive efficacy of progestin-only implants has been extensively studied and is attributed to alteration–suppression of ovulation and production of thick cervical mucus that is virtually impenetrable by spermatozoa. Preclinical toxicological data indicate that progestin-containing implants have similar profiles compared with oral contraceptives (Jordan, 2002). In addition, toxicological data are available to support the safety of Implanon in humans (Croxatto, 2002a; Jordan, 2002). Side effects are relatively rare but include spotting; irregular, prolonged, heavy, or infrequent vaginal bleeding; amenorrhea (Fraser et al., 1998); and reduction in serum ferritin concentrations (Faundes, Tejada, Brache, & Alvarez, 1987). Migraine and respiratory–cardiac abnormalities were reported, but there was no significant change in body weight or blood pressure (Akhter et al., 1993; Peralta, Diaz, & Croxatto, 1995). The major disadvantage of subdermal implants was surgical insertion and removal of the capsules–rods.

Among progestin-only subdermal LNG-containing implants, Norplant and Norplant II/Jadelle were most extensively studied. Norplant consists of a set of six small (2.4 mm $\times$ 34 mm) silicone capsules, each filled with 36 mg LNG with total LNG load of 216 mg approved for 5 years of use. The implants are inserted in a superficial plane beneath the skin of the upper arm. Norplant has been shown to produce peak plasma levels of 0.4–0.2 ng/ml up to the 8th year of treatment, with a mean of 0.28 ng/ml during the first 5 years (Peralta, Diaz, & Croxatto, 1995).

To assess the safety and tolerability of the Norplant system, Diaz, Pavez, Miranda, Johansson, and Croxatto (1987) followed 376 premenopausal women with Norplant implants for 8 years. The average LNG plasma levels declined steadily over the 8 years of use. Mean plasma levels were 0.35 ng/ml after the 1st year, 0.29 ng/ml after the 5th year, and 0.22 ng/ml after the 8th year. Fifty-six women who received the first implant and 10 women who accepted the replacement implants were terminated from the study because of bleeding problems and other side effects commonly observed in hormonal contraception. A second generation implant, Norplant II (LNG, Jadelle), contains only two rods versus six capsules (Norplant) and releases 50 g/day of LNG during 3 years of approved use. LNG's mean release rate in vivo is approximately 100 microgram/day after 1 month, followed by a decline to approximately 60 microgram/day after 12 months and approximately 30 microgram/day stabilized release after 24 months (Croxatto, 2002a, 2002b).

A 5-year randomized study compared Norplant II (LNG, Jadelle) and Norplant contraceptive implants in 1,198 women (Sivin et al., 1998). Both systems were well tolerated and reasons for discontinuation, such as vaginal spotting–bleeding, irregular bleeding, headache, weight gain, and acne, were similar in both groups, although slightly lower rates for rods versus capsules were reported (3.5/100 and 4.2/100, respectively). Compared with silicone capsules, complications and time for rod removal were at a lower rate for Norplant II.

Transdermal Administration of Synthetic Progestins

Transdermal delivery of synthetic progestins via ring, gel, patch, or spray as alternative methods for contraception are

increasingly common, well tolerated, and convenient to use; they also compare favorably with respect to the efficacy of oral contraceptives (Johansson, 2004; Sitruk-Ware, 2007b). For example, a 19-norprogesterone derivative, NES (previously known as ST-1435), is an orally inactive progestin with high progestational activity. It is available in both a vaginal ring formulation (Laurikka-Routti, Haukkamaa, & Heikinheimo, 1990) and transdermally (Haukkamaa, Laurikka-Routti, & Heikinheimo, 1991). To determine whether transdermal progesterone administration produces clinically efficacious serum concentrations, Haukkamaa et al. (1991) administered single doses of 2.3, 4.5, and 9 mg of commercial gel (Pregestogel) transdermally to 6 healthy women during the late luteal phase. Transdermal absorption reached serum concentrations of 232 pmol/l, high enough for therapeutic purposes. Concentrations 24 hr after application were still high as a result of sustained release of the steroid from the skin. No side effects or adverse events were reported (Haukkamaa et al., 1991). Other studies have shown similar results, although there were reports of irregular bleeding (Laurikka-Routti, Haukkamaa, & Lahteenmaki, 1992). No other side effects or adverse events were reported.

Another transdermal method of steroid delivery for contraceptive purposes is accomplished using a patch (Ortho Evra/Evra). It is typically applied to the skin of the upper outer arm, abdomen, torso, or buttocks once a week for 3 consecutive weeks, followed by a patch-free week for monthly withdrawal bleeding. A 20-cm (2) transdermal patch is estimated to deliver 150 μg of norelgestromin (the active metabolite of norgestimate) and 20 μg of ethinyl estradiol daily into the systemic circulation. Single and multiple applications of the patch produce stable daily serum concentrations of both steroids in ranges similar to oral norgestimate (Ortho-Cycle/Cilest: 250 μg/ethinyl estradiol 35 μg) for up to 10 days and are therefore clinically efficacious. These levels are maintained under hot and humid conditions and during exercise and cool water immersion and do not depend on the site of application. In addition, no alterations were observed in norelgestromin and ethinyl estradiol pharmacokinetics after tetracycline coadministration in eight trials where a once-weekly contraceptive patch (Ortho Evra/Evra) was used (Abrams, Skee, Natarajan, & Wong, 2002). The side-effect spectrum is similar to oral contraceptives, although slightly higher rates of breakthrough bleeding were reported in the first 1–2 months with the transdermal patch. Mild skin reactions were also reported, which resulted in discontinuation rates under 2% (Abrams et al., 2002; Audet et al., 2001).

Intrauterine Administration of Synthetic Progestins

Direct intrauterine delivery of progestins has been commonly used because it is convenient, ensures compliance, and permits avoidance of the first-pass metabolism. The intrauterine system (LNG IUS) is marketed as Mirena, with LNG as an active ingredient. Mirena is a small plastic T-shaped device containing a 1:1 ratio of 52 mg LNG and polydimethylsiloxane, a carrier polymer (Abu, Brown, & Ireland, 2006). The system releases 20 μg LNG daily for the first 5 years (Pakarinen & Luukkainen, 2005). Maximum serum levels of 150–200 pg/ml are typically reached within a few hours. Twenty-six percent of women who used the LNG IUS reported no bleeding after 12 months; this was usually attributed to the antiproliferative action of the active substance, which decreases menstrual blood loss. In a follow-up study to assess the long-term effects of the LNG-IUS system (Ronnerdag & Odlind, 1999), 100 patients agreed to continue its use and a second IUD was introduced. At the end of the 5-year cycle, 82 continued their participation for an additional 5 years and a third IUD was inserted. Amenorrhea was achieved in 26% of patients (90-day reference period) in the first of two 5-year cycles. Many women became amenorrheic soon after the third IUD was introduced. At the end of the study, 60% of the study subjects reported amenorrhea. Side effects included spotting, increases in hemoglobin concentration, increases in blood pressure, and weight gain (Ronnerdag & Odlind, 1999). The effect of the LNG IUDs is localized to the endometrium, therefore pituitary and ovarian functions are not affected (Sitruk-Ware, 2007a). This system is designed to be replaced every 5 years. No other side effects were reported, in contrast to the copper T380A IUD that was associated with increased menstrual bleeding (Luukkainen et al., 1987). Clinical trials reported discontinuation because of side effects, such as expulsion, bleeding problems, pain, and hormonal effects. Other side effects, such as increases in weight and blood pressure, were also reported. IUSs were removed because of weight gain, mood disturbance, pain, and bleeding (Inki, 2007; Wildemeersch, 2007; Wildemeersch & Rowe, 2005). Bone mass was not affected by this contraceptive method (Inki, 2007).

In a recent clinical trial to assess safety, contraceptive efficacy, and convenience of use, the newer LNG IUS system, Femilis, was studied in 235 premenopausal women. Femilis is a novel device that releases 20 μg of LNG per day (Wildemeersch & Rowe, 2005). It is available in two sizes, Femilis and Femilis Slim. Subjects were divided into two groups: 143 women who had previously given birth (parous) received Femilis, and 92 women who had never given birth (nulliparous) received Femilis Slim for 1 year. This system was generally well tolerated. Bleeding and pain were reported in 10 cases in which the IUD was removed (Wildemeersch & Rowe, 2005).

New IUDs are designed to avoid the common side effects of expulsion, pain, and abnormal bleeding. These are termed "frameless" devices and fit more easily in the uterine cavity. Side effects of these devices also include increased menstrual bleeding, pain, and expulsion, but these are less pronounced than in the case of the earlier IUDs. One frameless LNG IUS, marketed as FibroPlant, was reported to deliver 20 μg LNG daily over a 5-year period. No serious adverse effects were reported during clinical trials of this study beyond those described above (Wildemeersch, 2007).

Parenteral Administration of Synthetic Progestins

The synthetic progestin Depo-Provera is commonly used for long-term contraception as well as for other clinical applications, as discussed above. Depo-Provera typically

contains 150 mg depot-MPA (DMPA) and has been reported to decrease the risk of endometrial cancer, iron deficiency, anemia, and pelvic inflammatory disease. Common side effects include weight gain, mood changes, and menstrual pattern alterations (Aktun et al., 2005; Westhoff, 2003).

In a clinical trial to investigate the safety and tolerability of depot-medroxyprogesterone acetate (DMPA) 9,262 women received injections of 150 mg DMPA every 12 weeks for up to 3 years. This dose of DMPA was generally well tolerated. The most common side effects and reasons for discontinuation included menstrual alterations, weight gain, bloating, breast pain and enlargement, headache, mood changes, sexual dysfunction, and acne (Aktun et al., 2005).

In another study with similar goals, 1,056 premenopausal women received injections of same-day DMPA over a 2-year study period. Eighty-one percent of the initial injections were administered the same day (outside the first 5 days since the onset of menses). This treatment regimen was safe and efficient, and effective contraception was available within 7 days of administration. No adverse events or side effects of DMPA administration were reported in this study (Nelson & Katz, 2007).

Another longitudinal study was carried out in 917 women who received a DMPA injection once every 3 months (Sadeghi-Bazargani et al., 2006). Forty-eight percent of the subjects (444 of 917) discontinued DMPA injections before the study ended, mainly because of irregular menstrual bleeding and cessation of menses. DMPA users with a history of cesarean section experienced a higher rate of bleeding complications. Despite this, the lower discontinuation rate in the DMPA group was statistically significant ($p < .05$) in comparison with the placebo group, where almost 90% of subjects discontinued use (Sadeghi-Bazargani et al., 2006). All of the above studies are summarized in Table 1.

Natural Progesterone

Natural progesterone can be administered by oral, intranasal, transdermal, vaginal, and rectal routes or by intravenous or intramuscular injection. Oral preparations of natural progesterone have been proven to be inferior to intramuscular and vaginal routes (Tavaniotou, Smitz, Bourgain, & Devroey, 2000) because of the low absorption rates and rapid clearance rates (Maxson & Hargrove, 1985; Simon et al., 1993). Intranasal progesterone administration was shown to be effective in reaching therapeutic levels in 10 healthy menopausal women. There was no evidence of nasal irritation, but all subjects complained of the unpleasant taste of the spray (Cicinelli et al., 1991). Transdermal progesterone administration in a cream did not produce a biological effect on the lipid levels, bone mineral metabolic markers or density, or mood, but there is conflicting evidence with respect to vasomotor symptoms (Leonetti, Longo, & Anasti, 1999; Wren, Champion, Willetts, Manga, & Eden, 2003). Intravenous (Kumar, Goodno, & Barnes, 1963; Taubert & Haskins, 1963), intramuscular (de Wit et al., 2001; Soderpalm et al., 2004), and rectal routes of progesterone administrations are inconvenient, especially for long-term clinical use, and may produce some side effects (de Lignieres, 1999).

Intravaginal Administration of Natural Progesterone

Intravaginal progesterone administration is clinically useful for chronic administration and involves insertion of progesterone gels, rings, or suppositories–pessaries (Sitruk-Ware, 2007b). This route of progesterone administration has advantages, such as absence of local pain, avoidance of first-pass hepatic metabolism, rapid absorption, sustained plasma concentrations, high bioavailability, and local endometrial effect (von Eye Corleta, Capp, & Ferreira, 2004). Several studies have demonstrated that vaginally administered progesterone reached levels that are similar to those obtained in ovulatory and luteal phases (Archer et al., 1995; Nillius & Johansson, 1971; von Eye Corleta et al., 2004). To further evaluate the bioavailability of progesterone after intravaginal administration, von Eye Corleta et al. (2004) administered vaginal suppositories containing 25, 50, or 100 mg progesterone to 35 healthy ovulating patients in the follicular phase of the menstrual cycle (von Eye Corleta et al., 2004). Progesterone serum concentrations reached maximal levels within 2 or 3 hr after the administration and were similar for the three groups (7.27 ± 2.8 ng/ml; 8.84 ± 3.14 ng/ml; 9.82 ± 9.8 ng/ml, respectively). In another study, vaginal suppositories of 100 mg progesterone produced a rapid increase in plasma progesterone levels, which peaked between 9.5 ng/ml and 19.0 ng/ml within 4 hr, then gradually decreased over the next 8 hr (Nillius & Johansson, 1971). Some side effects of intravaginal progesterone administration include drowsiness, decrease in libido, dyspareunia, vaginal irritation, vaginal bleeding or spotting associated with cramps, breast tenderness, fatigue, pruritus, irritability, and local warmth (Archer et al., 1995; Pouly et al., 1996). Micronized vaginal creams have been developed in an effort to overcome these problems (Kimzey, Gumowski, Merriam, Grimes, & Nelson, 1991).

Rectal Administration of Natural Progesterone

Rectal preparations of natural progesterone are currently available as an alternative to vaginal suppositories in conditions of vaginal infection, cystitis, recent childbirth, or when barrier contraception methods are used. Plasma progesterone concentrations were reported to be similar after administration of either rectal or vaginal suppositories (Nillius & Johansson, 1971; Tay & Lenton, 2005). Progesterone's capacity for luteal support was compared after vaginal and rectal administration in women of childbearing age (Tay & Lenton, 2005). Three different progesterone preparations were administered: Cyclogest ($n = 35$) rectally and Ultrogesten ($n = 55$) and Crinone ($n = 36$) vaginally. Plasma progesterone levels were reported to be similar in all three groups despite the differences in the route of administration and ranged between 26–23 nmol/l. No side effects were reported in this study.

A comparison of vaginal and rectal administration of progesterone (pregn-4-ene-3, 20-dione) in suppository form to

Table 1
Synthetic Progestins: Dose, Formulation, Route of Administration, Regimen, Plasma Levels, and Side Effects

Dose and formulation	Route of administration	No. of subjects	Regimen	Plasma level	Side effect	Reference
0.5 mg norethindrone acetate	Oral	24 postmenopausal women	Single dose	19.3 nmol/l	None reported	Stadberg et al. (1999)
5 mg nomegestrol acetate	Oral	36 premenopausal women	Daily, Days 7 to 25 of cycle for 6 cycles	8 ng/ml	Increased antithrombin, decreased triglycerides	Basdevant et al. (1991)
160 mg megestrol acetate or micronized megestrol acetate	Oral	24 males	Single dose of one or the other	40 ng/ml conventional; 110 ng/ml micronized	None reported	Farinha et al. (2000)
10 mg Provera (MPA)	Oral	6 males	Daily for 1 week	Not reported	Sluggishness	Little et al. (1974)
216 mg Norplant (LNG)	Subdermal implant	1,198 premenopausal women	Single dose lasts up to 8 years	Not reported	Vaginal spotting-bleeding, irregular bleeding, headache, weight gain, acne	Sivin et al. (1998)
140 mg Norplant II (LNG)	Subdemal implant	1,198 premenopausal women	3 years	Not reported	Vaginal spotting-bleeding, irregular bleeding, headache, weight gain, acne	Sivin et al. (1998)
216 mg Norplant (LNG)	Subdermal implant	376 premenopausal women	Single dose lasts up to 8 years	1st year: 0.35 ng/ml; 2nd year: 0.29 ng/ml; 8th year: 0.22 ng/ml	Bleeding, etc.	Diaz et al. (1987)
2.3, 4.5, and 9 mg Nestorone	Transdermal gel	6 premenopausal women	Single dose	232 pmol/l	Irregular bleeding	Haukkamaa et al. (1991)
150 mg Depo-Provera (MPA)	Intramuscular injection	917 premenopausal women	Once every 12 weeks	Not reported	Irregular bleeding, menstrual cessation	Sadeghi-Bazargani et al. (2006)
150 mg Depo-Provera (MPA)	Intramuscular injection	9,262 premenopausal women	Once every 12 weeks	Not reported	Menstrual disturbances, weight gain, bloating, breast enlargement-pain, headache, mood change, sexual difficulties, acne	Aktun et al. (2005)
60 mg Femilis (LNG)	Intrauterine	143 premenopausal women (parous)	20 μg daily for 1 year	Not reported	Mild pain during insertion, expulsion, bleeding, pain	Wildemeersch & Rowe (2005)
60 mg Femilis Slim (LNG)	Intrauterine	92 premenopausal women (nulliparous)	20 μg daily for 1 year	Not reported	Mild pain during insertion, expulsion, bleeding, pain	Wildemeersch & Rowe (2005)
LNG-IUS (LNG)	Intrauterine	100 premenopausal women	20 μg daily for 1 year	Not reported	Spotting, increase in hemoglobin concentration, increase in blood pressure, weight gain	Ronnerdag & Odlind (1999)

premenopausal women also found no significant differences in mean plasma progesterone levels (Nillius & Johansson, 1971). Specifically, mean plasma progesterone levels reached 13.5 ng/ml after vaginal administration ($n = 6$) and 22.5 ng/ml after rectal administration ($n = 6$) of the same dose of progesterone. Peak plasma progesterone levels were reported to coincide with pronounced side effects, such as nausea, depression, and other early pregnancy-like symptoms.

Furthermore, progesterone plasma levels were compared between postmenopausal women ($n = 3$) and men ($n = 3$) after rectal administration of two preparations of natural progesterone in a suppository form: Cyclogest (200 mg) and pharmacy-made suppositories in Witepsol HIS with 200 mg active substance. There were no significant differences between the average plasma progesterone levels after administration of either form of suppository or between men and women. Specifically, women produced average plasma levels of 64.2 nmol/l and 61.6 nmol/l 6 hr after administration of Witepsol HIS and Cyclogest, respectively. Similarly, 64.7 nmol/l and 62.4 nmol/l plasma concentrations of progesterone were documented in men 6 hr after administration of Witepsol HIS and Cyclogest, respectively. No adverse events or side effects were reported in this study (van der Meer, van Loenen, Loendersloot, & Jaszmann, 1982).

Intramuscular Administration of Natural Progesterone

There are few clinical applications for intramuscular progesterone administration, but it is often used in clinical laboratory studies of the subjective and physiological effects of progesterone. The sedative side effects of natural intramuscular progesterone were examined in healthy women and men (Soderpalm et al., 2004). Single doses of 200 mg progesterone suspended in peanut oil were administered by intramuscular injections in the upper arms. These injections were given once a month for 2 months to women during the early follicular phase of the menstrual cycle. In men, the two sessions where they received progesterone injections were scheduled at least 1 week apart. Peak plasma levels of progesterone were detected at approximately 3 hr after administration and averaged 194 ng/ml for men and 270 ng/ml in women. There were no significant sex differences in plasma levels of progesterone. Six of the 17 subjects reported mild to moderate pain at the injection site. Two subjects had elevated temperatures after progesterone injection but recovered quickly after treatment with Tylenol. In addition, some subjects reported increased fatigue, but other measures of subjective effects (a profile of mood states, Visual Analog Scale (VAS) measures of subjective effects, word recall, and Digit Symbol Substitution Test (DSST) measures of motor and cognitive impairment) were unaffected. Physiological effects of progesterone included an elevation of heart rate in women and a decrease in performance of smooth pursuit eye movements (a sensitive measure of motor impairment) in both men and women. Similar mild sedative effects were also reported in previous studies by the same group (de Wit et al., 2001). Progesterone levels were much higher than those observed in normally cycling women during the luteal phase or in patients taking progesterone for clinical use (Soderpalm et al., 2004). The major adverse side effects involved pain at the site of intramuscular injection.

Another study examined the sedative side effects of intramuscular progesterone administration in postmenopausal and normal cycling women (de Wit et al., 2001). A single injection of intramuscular progesterone suspended in sesame oil was administered to both groups. Postmenopausal women received 25, 50, or 100 mg im progesterone during four 13-hr sessions at 1-week intervals. The normally cycling women only received the 100-mg dose during two 13-hr sessions conducted during the early follicular phase of two menstrual cycles. Each progesterone dose was administered intramuscularly in the upper arm. There was a progesterone dose-dependent increase in plasma levels measured in postmenopausal women: 16.9 ng/ml after 25-mg dose, 36.5 ng/ml after 50-mg dose, and 83.8 ng/ml after 100-mg dose. In women with normal cycles, the peak plasma level after the 100-mg dose of progesterone was 81.8 ng/ml. Only minimal sedative side effects were detected after all doses of progesterone (de Wit et al., 2001).

The above-described clinical studies had a number of limitations, including small sample size and, at times, nonrandomized and nonblind designs. However, high efficacy and lack of significant adverse effects were observed overall after administration of synthetic progestins and natural progesterone.

It is important to note that although progesterone and synthetic progestins are used for similar purposes, these may not exert similar modulatory effects on target organs, and each progestin molecule may have specific effects on neuroendocrine action (Bernardi et al., 2006). For example, a commonly used progestin, MPA, was shown to induce more negative somatic effects, more reports of breast tenderness, and increased magnitude and duration of vaginal bleeding in comparison with natural (micronized, oil-suspended) progesterone in early menopausal women (Cummings & Brizendine, 2002). MPA and natural progesterone also were found to differ with respect to molecular signaling in human endothelial cells, suggesting that there may be differential cardiovascular effects (Simoncini et al., 2004). All of the above-referenced studies are summarized in Table 2.

Micronized Natural Progesterone

Since 1980, another form of natural progesterone, micronized natural progesterone, has been clinically available and is typically administered orally (de Lignieres, 1999; Simon et al., 1993). Micronized natural progesterone is chemically identical to the naturally produced progesterone in humans and is postulated to exhibit better absorption–bioavailability after oral administration than natural progesterone (de Lignieres, 1999; Simon et al., 1993). Although progesterone is known to produce dysphoric mood changes, sedation, and fatigue, as well as to reduce mental acuity, positive and even protective properties of this steroid on some cardiovascular pathologies (e.g., hypertension and coronary artery disease), reproductive benefits (e.g., pregnancy sustainability), and attenuation of stimulant drug-related positive subjective responses (Evans & Foltin, 2006; Germond et al., 2002; Rylance et al., 1985; Sofuoglu et al., 2002; Sofuoglu et al., 2004; Tavaniotou et al., 2000) were also reported. Studies of orally and parenterally administered micronized progesterone have examined its bioavailability, efficacy, safety, and tolerability (Dennerstein et al.,

Table 2
Natural Progesterone: Dose, Formulation, Regimen, Route of Administration, Plasma Levels, and Side Effects

Dose and formulation	Route of administration	No. of subjects	Regimen	Plasma level	Side effect	Reference
25, 50, or 100 mg	Intravaginal suppository	35 premenopausal women	Single dose	7.27 ng/ml; 8.84 ng/ml; 9.82 ng/ml	None reported	von Eye Corleta et al. (2004)
100 mg	Intravaginal suppository	6 premenopausal women	Single dose	9.5–19.0 ng/ml	None reported	Nillius & Johansson (1971)
25 or 100 mg	Rectal suppository	6 premenopausal women	Single dose	6.4 ng/ml; 22.5 ng/ml	None reported	Nillius & Johansson (1971)
100 mg	Rectal suppository	1 premenopausal woman	Once daily for 5 days	Average daily peak of 4.76 but was not stable	Nausea, depression, early pregnancy-like symptoms	Nillius & Johansson (1971)
200 mg Cyclogest	Rectal suppository	3 postmenopausal women	Single dose	61.6 nmol/l	None reported	van der Meer et al. (1982)
200 mg Generic P	Rectal suppository	3 postmenopausal women	Single dose	64.2 nmol/l	None reported	van der Meer et al. (1982)
200 mg Cyclogest	Rectal suppository	3 men	Single dose	62.4 nmol/l	None reported	van der Meer et al. (1982)
200 mg Generic P	Rectal suppository	3 men	Single dose	64.7 nmol/l	None reported	van der Meer et al. (1982)
200 mg	Intramuscular injection	7 premenopausal women	Once a month for 2 months	270 ng/ml	3 women reported local pain at injection site/ elevated temperature and fatigue	Soderpalm et al. (2004)
200 mg	Intramuscular injection	10 men	Once a week for 2 weeks	194 ng/ml	3 men reported local pain at injection site/elevated temperature and fatigue	Soderpalm et al. (2004)
100 mg	Intramuscular injection	8 premenopausal women	Once a month for 2 months	81.8 ng/ml	Decreased ratings of vigor, friendliness, and arousal	de Wit et al. (2001)
25, 50, or 100 mg	Intramuscular injection	10 postmenopausal women	Once a week for 4 weeks	16.9 ng/ml; 36.5 ng/ml; 83.8 ng/ml	Increased ratings of sluggish	de Wit et al. (2001)
50 mg	Intramuscular injection	15 postmenopausal women	Once daily for 2 days	14.3 ± 1.0 ng/ml	None reported	Simon et al. (1993)

1985; Evans & Foltin, 2006; Gron et al., 1997; Rylance et al., 1985; Simon et al., 1993; Sofuoglu et al., 2002, 2004; Tollan et al., 1993).

Oral Administration of Micronized Natural Progesterone

A number of clinical studies closely examined beneficial and adverse effects of oral micronized natural progesterone after both acute and chronic administration. Some illustrative studies are summarized below.

Acute oral micronized natural progesterone administration studies. Sedative and cognitive attenuating properties of progesterone were further studied in several clinical studies using the oral micronized form. Although it only takes approximately 150 mg oral micronized progesterone to reach normal midluteal phase levels in premenopausal women (de Lignieres, 1999), postmenopausal women (Rylance et al., 1985; Simon et al., 1993), and men (Evans & Foltin, 2006; Rylance et al., 1985), oral micronized progesterone has been administered at much higher doses in some studies (Freeman et al., 1992). The effects of placebo and 300, 600, and 1,200 mg oral micronized progesterone on mood and performance were examined in 24 healthy premenopausal female subjects, ages 18–24 years (Freeman et al., 1992). These acute doses of progesterone produced average peak plasma progesterone concentrations of 9.01, 32.81, and 58.54 ng/ml, respectively, at 2 hr after administration. Psychometric tests and mood scales were conducted at baseline and once each hour following progesterone administration. Oral progesterone was associated with dose-dependent increases in reports of fatigue and dose-dependent decreases in vigor, but performance deficits were recorded in only 2 of 24 subjects, who scored lower on psychometric tests. These subjects had the highest plasma progesterone levels at the 1,200-mg dose. No other adverse

effects were reported in this study after the acute administration of oral micronized progesterone over this dose range.

Sedative effects of oral micronized progesterone on cognitive performance the morning after administration of a single 300-mg dose of progesterone were examined in 10 healthy male volunteers (Gron et al., 1997). Progesterone po was administered at two different study visits separated by at least 1 week. Peak plasma levels reached approximately 23 ng/ml at the time of cognitive testing. Cognitive examinations included global indexes of cognitive speed and attentional flexibility, such as Zahlenverbindungstest (the German version of the Trail Making Test) and Geteilte Aufmerksamkeit (Divided Attention Test). No consistent effects of progesterone on cognitive performance were detected. No other adverse effects were reported after the administration of 300 mg oral micronized progesterone in these men.

In another study, progesterone's effects on drug-related subjective responses were studied in women (Sofuoglu et al., 2002). Because progesterone levels are typically high in the luteal phase and low in the follicular phase, it is important to note that this study controlled for menstrual cycle phase as confirmed by low baseline levels of endogenous progesterone. To examine progesterone's effect on subjective responses to smoked cocaine, Sofuoglu et al. (2002) administered 5 women a single dose of 200 mg oral micronized progesterone or placebo during the early follicular phase of the menstrual cycle. Two hours later, subjects received three deliveries of 0.4 mg/kg smoked cocaine separated by 30 min each. Progesterone treatment did not significantly affect blood pressure and heart rate increases in response to cocaine; however, subjective measures showed a diminished rating of "feel the effect of the last dose," indicating attenuation of some of the subjective effects of cocaine. A later study by the same group assessed the safety and tolerability of progesterone treatment in both men and women, as well as its influence on subjective responses. Six male and 4 female cocaine users received two doses of 200 mg progesterone before a self-administration period of 0.3 mg/kg cocaine. In this study, progesterone treatment attenuated cocaine-induced increases in diastolic blood pressure but not systolic blood pressure or heart rate. Subjective ratings of "high" and "feel the effect of the last dose" were also attenuated but did not alter cocaine self-administration behavior (Sofuoglu et al., 2004). Limitations of these studies included small sample size as well as the administration of only single acute doses of progesterone. Dose-dependent effects of progesterone administration on mood and cognitive performance were investigated in only one study (Freeman et al., 1992).

Chronic dose studies. Few clinical studies have investigated multiple doses of progesterone administered chronically. A novel oral compound containing the micronized form of progesterone (Utrogestan) was tested for better bioavailability and was postulated to be devoid of adverse metabolic effects commonly associated with synthetic progestins (Simon et al., 1993). Three doses of oral micronized progesterone (100, 200, and 300 mg) were administered to 15 postmenopausal women once a day for 5 days. A dose-dependent increase in the maximum progesterone levels of 6.5, 13.8, and 32.2 ng/ml was documented. Observed progesterone levels were comparable with normal levels of progesterone reported in premenopausal women during the midluteal phase of their menstrual cycle (Carmina & Lobo, 2004; Strauss, 2004). The mean terminal half-life was between 16.2 and 18.3 hr at all three doses and did not differ significantly among study subjects. However, peak progesterone plasma levels were significantly greater and relative bioavilability of oral micronized progesterone was twice as high when progesterone administration was followed by food intake. In this study, the doses of oral micronized progesterone did not affect cholesterol, aldosterone synthesis, blood pressure, or mood. In addition, this study compared the absorption of 200 mg oral micronized progesterone with 50 mg intramuscular progesterone. The intramuscular progesterone produced higher serum progesterone levels (14.3 ng/ml) than did the oral micronized progesterone (4.3 ng/ml) when dose was normalized (Simon et al., 1993).

Considering the sodium-excreting properties of progesterone (Pechere-Bertschi & Burnier, 2007), no reduction in blood pressure was reported in another study that explored the effects of administration of the same compound (Utrogestan) on the circulatory system (Tollan et al., 1993). Twelve healthy men were given four doses of 100 mg oral micronized natural progesterone daily for a period of 10 days. Blood samples for analysis of progesterone levels were obtained before, during, and after the oral administration period. After 5 days of 400 mg total daily doses of progesterone, plasma levels peaked at 30 nmol/l, the approximate level of plasma progesterone reported during the luteal phase of the menstrual cycle. After 10 days of the 400-mg dose schedule, average plasma levels of progesterone were measured at 25 nmol/l. Systolic and diastolic blood pressure, catecholamine plasma levels, and transcapillary fluid balance were recorded as measures of effects on the circulatory system. Blood pressure, weight, and fluid balance, as well as testosterone concentrations, hemoglobin, and hematocrit were not affected by progesterone administration. However, a significant decrease in venous plasma levels of noradrenaline was reported, although arterial noradrendaline and adrenaline levels remained unchanged. No adverse effects of oral progesterone administration were reported after administration of cumulative daily doses of 400 mg (100 mg four times a day) progesterone each day for a 10-day period (Tollan et al., 1993).

Antihypertensive properties of oral natural progesterone were examined after chronic administration of 100, 200, and 300 mg oral micronized progesterone twice daily to 6 men and 4 postmenopausal women over a 6-week period (Rylance et al., 1985). The plasma levels of progesterone at the 200-mg dose were equivalent to concentrations during the luteal phase of the menstrual cycle, that is, 10 ng/ml (Carmina & Lobo, 2004; Evans & Foltin, 2006; Rylance et al., 1985; Strauss, 2004). No significant changes in weight or pulse were observed during this study. Two subjects reported mild lightheadedness 1 hr after ingestion of the two higher doses. No other adverse effects were reported after progesterone administration. As predicted, progesterone decreased blood pressure to normal levels in hypertensive subjects. Furthermore, the greater the dose of progesterone, the greater the reduction in blood pressure observed (Rylance et al., 1985).

Progesterone's effects on subjective drug responses were also examined in one study. The effect of three doses of 50

mg (150 mg total) oral micronized progesterone on subjective responses to smoked cocaine were investigated in male and female subjects (Evans & Foltin, 2006). Progesterone was administered twice a day for a total dose of 750 mg over 3 days. This cumulative dose regimen was chosen to mimic normal plasma progesterone levels in females during the midluteal phase of their menstrual cycle (10.0 ng/ml; Evans et al., 2002). No breakthrough bleeding or menstrual cycle disruption was documented after progesterone administration. In addition, no subjective reports of significant sedation were observed. These doses of oral micronized progesterone decreased the cocaine-induced increases in diastolic blood pressure and heart rate in both men and women and decreased the positive subjective effects of cocaine in women but not in men. This decrease in blood pressure in cocaine users after administration of progesterone is consistent with other clinical reports of chronic administration of progesterone (Rylance et al., 1985; Sofuoglu et al., 2004).

To assess the safety and tolerability of progesterone, as well as its effect on withdrawal bleeding, Shangold et al. (1991) administered two doses of oral micronized progesterone and placebo to 60 premenoupausal women with oligomenorrhea or amenorrhea. Subjects received a 10-day course of 200 mg (100 mg twice a day) or 300 mg (100 mg three times a day). Mean plasma concentrations of progesterone in subjects taking 300 mg daily were 12.6 $\pm$ 2.9 ng/ml in those who experienced withdrawal bleeding and 10.1 $\pm$ 2.1 ng/ml in those who did not experience withdrawal bleeding. Mean plasma concentrations of progesterone in subjects taking 200 mg daily were 4.8 $\pm$ 0.7 ng/ml and 3.2 $\pm$ 0.4 ng/ml, respectively. There were no major differences in adverse effects reported by women taking placebo or 200 mg/day or 300 mg/day oral micronized progesterone, with an average of 68% in each group reporting symptoms associated with progestational therapy. No significant differences between baseline and treatment levels of total cholesterol (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides) were reported in this study.

A double-blind study to investigate progesterone's proposed therapeutic effect on premenstrual mood disorder was conducted. Twenty-three premenopausal women diagnosed with PMS received 100 mg oral micronized progesterone in the morning and 200 mg oral micronized progesterone at bedtime for 10 days during the luteal phase of the menstrual cycle for 2 months (Dennerstein et al., 1985). Ten subjects who received progesterone treatment reported drowsiness, and 1 subject reported a migraine as a side effect of the medication. However, the authors noted improvements in PMS symptomatology. For example, subjects reported attenuation of negative mood symptoms, such as anxiety, depression, and stress. These changes in mood have also been seen in postmenopausal women given 200 mg oral micronized progesterone at bedtime (de Lignieres, 1999).

The major limitation of the above-mentioned studies of chronic progesterone administration was small sample size. Overall, no significant side effects were reported in these studies and the doses of progesterone administered for various clinical applications were demonstrated to be safe, tolerable, and, at times, beneficial in male and female volunteers.

Vaginal Administration of Micronized Natural Progesterone

Vaginal administration of micronized natural progesterone avoids first-pass hepatic metabolism and is used clinically in the majority of cases to support pregnancy. There are many such products on the market, including Crinone, Prochieve, Utrogestan, and Ellios. Nonliquefying vaginal creams containing micronized natural progesterone also provide an alternative to nonmicronized suppositories and have been shown to produce relatively reliable plasma levels (Kimzey et al., 1991). Vaginal gels (Crinone) with sustained release have also been developed and contain 45 or 90 mg progesterone in 1.125 g of gel with a polycarbophil base (Fanchin et al., 1997).

One study compared two vaginal formulations of micronized progesterone, Ellios (200 mg) and Utrogestan (100 mg), for luteal supplementation during the in-vitro fertilization (IVF) cycle (Germond et al., 2002). One hundred twenty-three premenopausal women were studied, and the treatment was generally well tolerated. Plasma progesterone levels peaked at Day 8 at approximately 60 nmol/l. There was no significant difference in the average plasma levels of progesterone between the two groups. Forty-three percent of the subjects receiving two 200-mg Ellios pessaries a day reported vaginal discharge, compared with 82% of the subjects receiving two 100-mg Utrogestan pessaries a day. Other common side effects, such as vaginal pruritus and drowsiness, were also reported more frequently by patients in the Utrogestan group than in the Ellios group. Subjects in both groups also reported a "feeling of coolness" without vaginal discharge.

Another study compared the pharmacokinetics of vaginally applied micronized progesterone gel (Crinone) and oral preparation of micronized progesterone (Prometrium; Levine & Watson, 2000). Six postmenopausal women sustained on estrogen therapy received a single dose of 90 mg progesterone gel. Peak plasma levels reached 10.51 $\pm$ 0.46 ng/ml within 8 hr. No changes in vital signs or electrocardiogram, clinical pathology, or other abnormalities were reported. Similar adverse effects as the oral micronized progesterone treatment group were observed, although particular side effects were not specified.

In conclusion, despite reports of minor side effects, several studies showed that vaginal preparations induce normal secretory mucosal transformation of the endometrium, even when plasma progesterone levels were relatively low, indicating a direct transit into the uterus—"first uterine pass effect" (Casanas-Roux et al., 1996; Fanchin et al., 1997; Germond et al., 2002; Levine & Watson, 2000).

Other Routes of Administration of Micronized Natural Progesterone

Sublingual, intramuscular, and rectal administrations of micronized progesterone were shown to achieve luteal phase serum concentrations with nonparenteral modes (Chakmakjian & Zachariah, 1987). The aforementioned studies are summarized in Table 3.

In summary, no significant side effects have been reported during chronic oral administration of micronized

Table 3
Micronized Natural Progesterone: Dose, Formulation, Regimen, Route of Administration, Plasma Levels, and Side Effects

Dose and formulation	Route of administration	No. of subjects	Regimen	Plasma level	Side effect	Reference
200 mg Ellios	Vaginal suppository	123 premenopausal women	Twice a day for 1 month	Peaked at Day 8 at about 60 nmol/l	Vaginal discharge, pruritus, drowsiness, coolness without vaginal discharge	Germond et al. (2002)
100 mg Utrogestan	Vaginal suppository	123 premenopausal women	Two capsules twice a day for 1 month	Peaked at Day 8 at about 60 nmol/l	Vaginal discharge, pruritus, drowsiness, coolness without vaginal discharge	Germond et al. (2002)
90 mg Crinone (8%)	Vaginal gel	6 postmenopausal women	Single dose	10.51 ± 0.46 ng/ml	Similar to oral micronized progesterone	Levine & Watson (2000)
150 mg	Oral	11 premenopausal women, 10 men	Twice a day for 3 days; 750 mg over 72 hr, followed by six doses of 6, 12, or 25 mg smoked cocaine	8.2 ng/ml women; 6.7 ng/ml men	None reported; decrease in cocaine-induced increases in diastolic BP & HR, and attenuated subjective effects in women, but not men	Evans & Foltin (2006)
200 mg	Oral	5 premenopausal women	Single dose; 2 hr later, three doses of 0.4 mg/kg smoked cocaine	Peaked at about 13 ng/ml	Attenuated subjective effects of cocaine; no effect on BP or HR	Sofuoglu et al. (2002)
300 mg	Oral	10 men	Single dose	23 ng/mL	None reported; no consistent effects on cognitive performance	van der Meer et al. (1982)
100, 200, and 300 mg	Oral	15 postmenopausal women	Once a day for 5 days	6.5 ng/ml; 13.8 ng/ml; 32.2 ng/ml	None reported	van der Meer et al. (1982)
100 mg	Oral	12 men	Four doses daily for 10 days	Day 5 at 30 nmol/l; Day 10 at 25 nmol/l	None reported; no changes in blood pressure, weight, testosterone concentration, hemoglobin, or hematocrit; decrease in venous plasma NEpi but not arterial NEpi or Epi	van der Meer et al. (1982)
300, 600, and 1,200 mg	Oral	24 premenopausal women	Single dose	9.01 ng/ml; 32.81 ng/ml; 58.54 ng/mL	Increased reports of fatigue, decreased reports of vigor	van der Meer et al. (1982)
200 mg	Oral	60 premenopausal women (oligomenorrheic or amenorrheic)	100 mg twice daily	4.8 and 3.2 ng/ml	68% in each group reported symptoms associated with progestational therapy	Soderpalm et al. (2004)
300 mg	Oral	60 premenopausal women (oligomenorrheic or amenorrheic)	100 mg three times daily for 10 days	12.6 and 10.1 ng/ml; patients with withdrawal bleeding-no bleeding	No change in total cholesterol, HDL, LDL, & TGL	
100, 200, and 300 mg	Oral	8 men, 4 postmenopausal women	Twice daily for 2 weeks at each dose; total = 6 weeks	Not reported	Two reports of mild lightheadedness; no change in HR or weight; decrease in BP	Soderpalm et al. (2004)
300 mg	Oral	23 premenopausal women	Daily for 10 days during luteal phase of two cycles	Not reported	Drowsiness (10), and one report of migraine; improvements in mood symptoms, such as anxiety, depression, and stress	de Wit et al. (2001)

Note. NEpi = norepinephrine; Epi = epinephrine; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HR = heart rate; BP = blood pressure.

natural progesterone doses of 100 mg/day (de Lignieres, 1999). There were no major differences in adverse effects reported by women taking placebo or 200 mg/day or 300 mg/day oral micronized progesterone (Shangold et al., 1991). In addition, in a placebo-controlled study, patients with premenstrual mood disorder did report drowsiness but reported improvements in anxiety, depression, and stress when given 100 mg oral micronized progesterone in the morning and 200 mg oral micronized progesterone at bedtime (Dennerstein et al., 1985). These positive improvements in mood have also been seen in postmenopausal women given 200 mg oral micronized progesterone at bedtime (de Lignieres, 1999). Taken together, these studies indicate that it is unlikely that any serious adverse side effects result from administration of single doses of up to 200 mg micronized natural progesterone to healthy men and women. Recent studies of oral administration of micronized natural progesterone (150–200 mg) to healthy men and women have not reported any adverse side effects other than mild fatigue, drowsiness, and lightheadedness (Dennerstein et al., 1985; Evans & Foltin, 2006; Freeman et al., 1992; Rylance et al., 1985; Sofuoglu et al., 2002, 2004).

Summary and Conclusions

As described above, progesterone is available in three formulations and a variety of preparations for different modes of administration. Progesterone has been shown to be safe and effective for many clinical applications. The therapeutic effects of progesterone and its neuroactive metabolites reflect interactions with serotonin, dopamine, *N*-methyl-D-aspartate, beta-endorphin, and sigma receptors (Pluchino et al., 2006; Schumacher et al., 2007). Recent advances in understanding the complex effects of progesterone have suggested new therapeutic applications (Schumacher et al., 2007). Clearly, further long-term investigations of progesterone are warranted.

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