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REF: Expediente 07-136-797

TÍTULO SOLICITADO: COMPOSICIONES Y MÉTODOS PARA EL TRATAMIENTO DE SÍNTOMAS RELACIONADOS CON EL CICLO.

PUBLICACIÓN: Gaceta: 592 de 30/05/2008, N° de publicación: 461.

PRIORIDAD: US 60/695.077 de 28/06/2005.

SOLICITANTE: WYETH.

APODERADO: ALVARO CORREA ORDOÑEZ.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comedidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La solicitud colombiana **07-136-797** que reivindica un método para tratar un sujeto hembra que presenta síntomas relacionados al ciclo menstrual que comprende administrar una cantidad efectiva de por lo menos un estrógeno y por lo menos una progestina, en donde dicha cantidad efectiva se administra diariamente durante por lo menos aproximadamente 100 días, carece de novedad y nivel inventivo como se argumenta a continuación:

En primer término, existen documentos que demuestran con anterioridad a la fecha de prioridad de la solicitud colombiana en trámite la combinación farmacológica entre estrógenos y progestinas en diversos regímenes para tratar dicha sintomatología relacionada al ciclo menstrual en la mujer, veamos:

❖ La publicación científica **Bleeding Patterns And Patient Acceptability Of Standard Or Continuous Dosing Regimens Of A Low-Dose Oral Contraceptive: A Randomized Trial¹** revela:

Abstract: The purpose of this study is to compare bleeding patterns and acceptability of a contraceptive regimen of combined 20 microg ethinyl estradiol/100 microg levonorgestrel taken with and without a hormone-free interval. Thirty-two women desiring oral contraception were randomized to six 28-day cycles (standard group) or 168 days without a pill-free interval (continuous group). Participants kept a daily bleeding calendar documenting bleeding events (none, spotting or required sanitary protection) and side effects (headache, nausea, breast tenderness, depression, premenstrual syndrome and bloating). Primary outcome was number of bleeding days. Secondary outcomes included bleeding days requiring sanitary protection, amenorrhea, patient acceptability of bleeding patterns, method satisfaction and affective side effects. There were no differences in the baseline characteristics of the two groups. Although total bleeding days were fewer in the continuous group (mean = 25.9 vs. 34.9 days), this result did not reach statistical significance. However, women in the continuous group reported significantly fewer bleeding days that required protection (18.4 vs. 33.8 days, $p < 0.01$), and were more likely to have amenorrhea. Although both groups reported a high level of satisfaction with bleeding patterns and side effect profiles, women in the continuous group reported significantly fewer days of bloating (0.7 vs. 11.1 days, $p = 0.04$), and menstrual pain (1.9 vs. 13.3 days, $p < 0.01$). Continuous use of 20 microg ethinyl estradiol/100 microg levonorgestrel is associated with less bleeding requiring protection, and more amenorrhea than standard administration. Taken with or without a hormone-free interval, this oral contraceptive formulation is highly acceptable with regard to bleeding patterns and side effect profile. The continuous group had fewer light and moderate bleeding days, less bloating and menstrual pain. For patients who are seeking these results, this method may be more desirable.

Por su parte la publicación científica **Continuous Combination Oral Contraceptive Pills To Eliminate Withdrawal Bleeding: A Randomized Trial²** revela:

¹ Kwiecien M, Edelman A, Nichols MD, Jensen JT. Contraception. 2003 Jan;67(1):9-13.

Abstract: *OBJECTIVE: To compare bleeding profiles of a traditional 28-day oral contraceptive pill cycle with continuous administration. METHODS: After a 28-day run-in cycle, women were randomized to either 28-day cycles (21 active pills and a pill-free week) or continuous use of the same 20 microg ethinyl estradiol/100 microg levonorgestrel formulation for 12 study cycles (336 days). The number of bleeding and spotting days were measured by daily diary. A subset underwent cycle 1 (n = 16), and nine (n = 14) pelvic ultrasound and endometrial histology sampling. Blood pressure, weight, hemoglobin, and adverse events were measured at revisit. The sample size with 80% power to detect a 67% reduction in bleeding days required 27 subjects in each arm. RESULTS: Of the 79 subjects randomized, 28 (70%) of the 28-day cycle and 32 (82%) of the continuous-use subjects completed the entire study (P = .6). With continuous use, 49%, 68%, and 88% of women reported no bleeding during cycles 2, 6, and 12, respectively. Amenorrhea or infrequent bleeding was present in 68% of continuous users during cycles 1-3 and increased to 88% during cycles 10-12. Spotting during cycle days 1-21 increased initially with continuous use but reduced over time, and by 9 months was less than the spotting reported by cyclic users. Adverse events, blood pressure, weight, and hemoglobin findings were similar between groups. CONCLUSION: Extension of the 28-day oral contraceptive cycle to continuous use with a low-estrogen dose combination oral birth control pill resulted in significantly fewer bleeding days.*

Si se tiene en cuenta que dentro de la sintomatología que revela la solicitud colombiana en trámite se encuentra la sintomatología física suave, moderada y severa, y que se menciona explícitamente la dismenorrea (cuyos síntomas pueden ser calambre en las piernas, dolor pélvico o abdominal intenso, dolor en la parte baja de las espaldas, dolor de cabeza, náuseas, mareos, vómitos, desmayos, diarrea o estreñimiento, fatiga, así como ansiedad, irritabilidad o depresión, expulsión durante la regla de coágulos de sangre), claramente puede observarse en estas publicaciones científicas que la combinación de un estrógeno y una progestina, específicamente etinilestradiol y levonorgestrel en rangos de dosis y tiempo que incluyen los mencionados por la solicitud colombiana en trámite, queda en evidencia la irrefutable carencia de nivel inventivo de dicha solicitud, al menos en estos aspectos.

❖ También existen publicaciones anteriores que revelan regímenes farmacológicos y formulaciones para el tratamiento de dicha sintomatología y que involucran las características esenciales de lo reivindicado por la solicitud colombiana, veamos:

- ✓ La patente americana US 2003/0139381 publicada el 24 de Julio de 2003 y titulada "ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY" revela:

² Miller L, Hughes JP. Obstet Gynecol. 2003 Apr;101(4):653-61.

[0024] The invention relates to oral contraceptives that will prevent pregnancy and diminish or eliminate PMS including PMDD. Methods of using these oral contraceptives to prevent pregnancy and diminish or eliminate PMS including PMDD are also provided. More particularly, the methods involve administering one of several combination oral contraceptive regimens. Importantly, these regimens do not contain pill-free or placebo intervals. (...)

[0033] The estrogens which may be employed as a component in the regimens of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens, including steroidal and nonsteroidal estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, ethynodiol diacetate, mestranol and quinestranol. Particularly of interest are 17 α -ethinyl estradiol and esters and ethers thereof. The preferred estrogen is 17 α -ethinyl estradiol. The natural estrogens may include, for example, conjugated equine estrogens, esterified estrogens, 17 β -estradiol, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate. (...)

[0034] The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17 α -ethinyltestosterone and derivatives thereof, 17 α -ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderone, ethisterone, cyproterone acetate, levonorgestrel, dl-norgestrel, d-17 α -acetoxy-13 β -ethyl-17 α -ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desogestrel and norgestimate. The preferred progestin is levonorgestrel. (...)

[0039] Pharmaceutical formulations or preparations containing the formulations of the invention and a suitable carrier can be solid dosage forms which includes tablets, dragees, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies, foams and controlled release depot entities; transdermals, vaginal rings, buccal formulations; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of estrogen, progestin and antidepressant as taught in this invention. (...)

1. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 81-89 consecutive days, followed by administration of estrogen for a period of 2-10 consecutive days.

2. The method of claim 1, in which the daily amount of estrogen administered for 81-89 consecutive days is equivalent to about 5-50 μg of ethinyl estradiol.

3. The method of claim 2, in which the daily amount of progestin administered for 81-89 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

4. The method of claim 3, wherein the combination of estrogen and progestin is administered for at least 84 consecutive days. (...)

21. The method of claim 16, in which the estrogen is ethinyl estradiol.

22. The method of claim 17, in which the progestin is levonorgestrel.

Como se puede apreciar claramente, en esta anterioridad se exponen absolutamente todos los aspectos fundamentales que resumen la invención reivindicada por la solicitud colombiana, específicamente lo relacionado con la combinación de los mismos estrógenos y las mismas progestinas y los intervalos de cantidades y de tiempos de los regímenes de dosificación, así mismo el tipo de formulaciones farmacéuticas que incluyen dicha combinación farmacológica, específicamente formulaciones sólidas para administración oral como lo son las cápsulas y las tabletas y formas transdérmicas y/o dispositivos de depósito.

✓ Por su parte la publicación internacional WO 2005/007112 publicada el 27 de enero de 2005 y titulada "METHODS OF HORMONAL TREATMENT UTILIZING CONTRACEPTIVE REGIMENS WITH CONTINUOUS ESTROGEN ADMINISTRATION" revela:

The present invention relates to methods of hormonal treatment that utilize contraceptive regimens involving administration of estrogen and progestin, followed by administration of estrogen.

(...)

Combinations of Progestin and Estrogen

Progestin	Norethindrone		Estrogen	EE Equivalent		P/E Ratio
	Dose (mg)	Dose (mg)		Dose (mg)	Dose (mg)	
Norethynodrel	9.85	9.85	Mestranol	0.150	0.105	93.810
	5.00	5.00		0.075	0.053	95.238
	2.50	2.50		0.036	0.025	99.206
	2.50	2.50		0.100	0.070	35.714
Norethindrone	10.00	10.00	Mestranol	0.060	0.042	238.095
	2.00	2.00		0.100	0.070	28.571
	1.00	1.00		0.050	0.035	28.571
	1.00	1.00		0.080	0.056	17.857
Norethindrone	1.00	1.00	Ethinyl estradiol (EE)	0.050	0.050	20.000
	1.00	1.00		0.035	0.035	28.571
	0.50	0.50		0.035	0.035	14.286
	0.40	0.40		0.035	0.035	11.429
Norethindrone acetate	2.50	2.50	EE	0.050	0.050	50.000
	1.00	1.00		0.050	0.050	20.000
	0.60	0.60		0.030	0.030	20.000
	1.50	1.50		0.030	0.030	50.000
Ethinodiol diacetate	1.00	1.00	Mestranol	0.020	0.020	50.000
	1.00	1.00		0.100	0.070	14.286
	1.00	1.00		0.050	0.050	20.000
	1.00	1.00		0.035	0.035	28.571
dl-Norgestrel	0.50	0.75	EE	0.050	0.050	10.000
	0.30	0.45		0.030	0.030	10.000
Levonorgestrel	0.10	0.35	EE	0.020	0.020	5.000
	0.15	0.52		0.030	0.030	5.000

Equivalencies
50 mg Mestranol = approx. 35 mg Ethinyl estradiol (EE)
0.1 mg dl-Norgestrel = approx. 0.15 mg Norethindrone

(...)

1. A method of reducing breakthrough bleeding in a female in need thereof, the method comprising administering to the female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

(...)

3. The method of claim 1, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

4. The method of claim 3, wherein the estrogen that is administered for a period of about 2 to about 10 days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

5. The method of claim 4, wherein the estrogen that is administered for a period of about 2 to about 10 days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

6. The method of claim 4, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

10. The method of claim 8, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

(...)

17. The method of claim 15, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

(...)

20. The method of claim 18, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

(...)

52. The method of claim 49, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

(...)

57. The method of claim 55, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

(...)

wherein said menstrual disorder is selected from the group consisting of irregular menstrual cycles, dysmenorrhea, and mittelschmerz.

En esta anterioridad se exponen absolutamente todos los aspectos fundamentales que se abordan en la invención reivindicada por la solicitud colombiana, específicamente lo referido a la combinación de los mismos estrógenos y las mismas progestinas, así como los intervalos de cantidades y de tiempos de los regímenes de dosificación.

En conclusión, la solicitud colombiana en trámite carece tanto de novedad como de nivel inventivo ya que la combinación de los agentes farmacológicos que reivindica para el tratamiento de la sintomatología asociada al ciclo menstrual en la mujer, resultan ser combinaciones descritas y ampliamente utilizadas para la misma finalidad en el estado de la técnica, además, dichas combinaciones farmacológicas se vienen usando en formulaciones farmacéuticas y para tratamientos terapéuticos, que de la misma manera, ya estaban ampliamente descritos en el mismo estado de la técnica.

❖ Por último, pero no por esto menos importante, es relevante resaltar que la solicitud colombiana en trámite, no solo carece de novedad y de nivel inventivo como se ha demostrado con los argumentos anteriores, sino que además incurre en una improcedencia directa de patentabilidad dado el hecho que en su capítulo reivindicatorio, específicamente en sus reivindicaciones 1 a 28, reivindica un método terapéutico lo cual es inaceptable a la luz de la Decisión 486 del año 2000

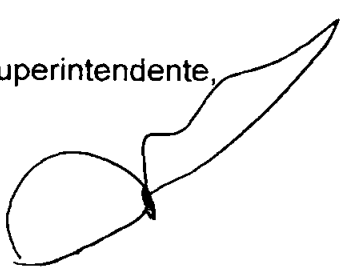
la cual expone explícitamente en su artículo 20 literal d) que *"No serán patentables (...) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."*

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

VI. ANEXOS

- ❖ Abstracts de todas las publicaciones científicas mencionadas en el acápite de Nuevos Argumentos.
- ❖ La patente americana US 2003/0139381 publicada el 24 de Julio de 2003 y titulada "ORAL CONTRACEPTIVES TO PREVENT PREGNANCY AND DIMINISH PREMENSTRUAL SYMPTOMATOLOGY" páginas 2, 4 y capítulo reivindicatorio.
- ❖ La publicación internacional WO 2005/007112 publicada el 27 de enero de 2005 y titulada "METHODS OF HORMONAL TREATMENT UTILIZING CONTRACEPTIVE REGIMENS WITH CONTINUOS ESTROGEN ADMINISTRATION" paginas 1, 41 y capítulo reivindicatorio.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

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☐ 1: Contraception. 2003 Jan;67(1):9-13.ELSEVIER Links
FULL-TEXT ARTICLE**Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomized trial.****Kwiecien M, Edelman A, Nichols MD, Jensen JT.**

Department of Obstetrics and Gynecology, Oregon Health and Science University, Mail Code L-466, Portland, OR 97201, USA.

The purpose of this study is to compare bleeding patterns and acceptability of a contraceptive regimen of combined 20 microg ethinyl estradiol/100 microg levonorgestrel taken with and without a hormone-free interval. Thirty-two women desiring oral contraception were randomized to six 28-day cycles (standard group) or 168 days without a pill-free interval (continuous group). Participants kept a daily bleeding calendar documenting bleeding events (none, spotting or required sanitary protection) and side effects (headache, nausea, breast tenderness, depression, premenstrual syndrome and bloating). Primary outcome was number of bleeding days. Secondary outcomes included bleeding days requiring sanitary protection, amenorrhea, patient acceptability of bleeding patterns, method satisfaction and affective side effects. There were no differences in the baseline characteristics of the two groups. Although total bleeding days were fewer in the continuous group (mean = 25.9 vs. 34.9 days), this result did not reach statistical significance. However, women in the continuous group reported significantly fewer bleeding days that required protection (18.4 vs. 33.8 days, $p < 0.01$), and were more likely to have amenorrhea. Although both groups reported a high level of satisfaction with bleeding patterns and side effect profiles, women in the continuous group reported significantly fewer days of bloating (0.7 vs. 11.1 days, $p = 0.04$), and menstrual pain (1.9 vs. 13.3 days, $p < 0.01$). Continuous use of 20 microg ethinyl estradiol/100 microg levonorgestrel is associated with less bleeding requiring protection, and more amenorrhea than standard administration. Taken with or without a hormone-free interval, this oral contraceptive formulation is highly acceptable with regard to bleeding patterns and side effect profile. The continuous group had fewer light and moderate bleeding days, less bloating and menstrual pain. For patients who are seeking these results, this method may be more desirable.

PMID: 12521651 [PubMed - indexed for MEDLINE]

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Review Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception [Rev. 2005]

Continuous oral contraceptives: are bleeding patterns dependent on the hormones given? [Obstet Gynecol. 2006]

Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial [Contraception. 2003]

Comparative study on intermittent versus continuous use of a contraceptive pill administered by oral route [Contraception. 1995]

Review Individualization of low-dose oral contraceptives. Pharmacological principles and practical indications for oral contraceptives [Minerva Ginecol. 2007]

» See Reviews... | » See All...

Patient Drug Information

Estrogen (Cenestin®, Enjuvia®, Estrace®, ...)

Estrogen is used to treat hot flashes ('hot flashes'; sudden strong feelings of heat and sweating) in women who are experiencing menopause ('change of life', the end of monthly menstrual periods). Some brands of estrogen...

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Continuous Combination Oral Contraceptive Pills to Eliminate Withdrawal Bleeding: A Randomized Trial

Leslie Miller, MD, and James P. Hughes, PhD

OBJECTIVE: To compare bleeding profiles of a traditional 28-day oral contraceptive pill cycle with continuous administration.

METHODS: After a 28-day run-in cycle, women were randomized to either 28-day cycles (21 active pills and a pill-free week) or continuous use of the same 20- μ g ethinyl estradiol/100- μ g levonorgestrel formulation for 12 study cycles (336 days). The number of bleeding and spotting days were measured by daily diary. A subset underwent cycle 1 ($n = 16$), and nine ($n = 14$) pelvic ultrasound and endometrial histology sampling. Blood pressure, weight, hemoglobin, and adverse events were measured at revisit. The sample size with 80% power to detect a 67% reduction in bleeding days required 27 subjects in each arm.

RESULTS: Of the 79 subjects randomized, 28 (70%) of the 28-day cycle and 32 (82%) of the continuous-use subjects completed the entire study ($P = .6$). With continuous use, 49%, 68%, and 88% of women reported no bleeding during cycles 2, 6, and 12, respectively. Amenorrhea or infrequent bleeding was present in 68% of continuous users during cycles 1–3 and increased to 88% during cycles 10–12. Spotting during cycle days 1–21 increased initially with continuous use but reduced over time, and by 9 months was less than the spotting reported by cyclic users. Adverse events, blood pressure, weight, and hemoglobin findings were similar between groups.

CONCLUSION: Extension of the 28-day oral contraceptive cycle to continuous use with a low-estrogen dose combination oral birth control pill resulted in significantly fewer bleeding days. (Obstet Gynecol 2003;101:653–61. © 2003 by The American College of Obstetricians and Gynecologists.)

From the Departments of Obstetrics & Gynecology and Biostatistics, University of Washington, Seattle, Washington.

This investigator-initiated study was funded by Wyeth Laboratories, Philadelphia, Pennsylvania.

An abstract of preliminary findings was presented by poster at The American College of Obstetricians and Gynecologists annual meeting, Chicago, 2001, and final conclusions were presented by poster at The American College of Obstetricians and Gynecologists annual meeting, Los Angeles, 2002.

We acknowledge Erika Lease and Savannah Stout, our study coordinators, for collecting the data and making the research happen.

The combination oral contraceptive (OC) is currently packaged and labeled for cyclic use with 21 hormone or active pills followed by seven spacer or placebo pills, to produce monthly withdrawal bleeding. This bleeding can signal the absence of pregnancy but is not essential to the contraceptive mechanism of the OC. In fact, stopping the progestin for 7 days allows ovarian follicular development and can contribute to method failure. Under the influence of the OC, the endometrium is typically thin, atrophic, protected against future endometrial cancer, and not in need of monthly shedding.¹

In spite of early research² with continuous OC administration, the original marketed OC was designed to appear “natural” in the hopes it would be viewed by the Catholic Church as a “morally permissible variant of the rhythm method,” and this required a lunar or monthly cycle.³ Twenty-six years ago, Loudon et al demonstrated that a withdrawal bleed every 3 months was acceptable and effective, but still no change in the OC schedule was introduced.⁴ Recently, the medical requirement to menstruate while on the pill has been questioned, and it has been suggested that women could skip the spacer pills to prevent bleeding.^{5–7} A recent review⁸ concluded that there is a lack of evidence regarding the best formulation, duration of active pill use, and the long-term effects of continuous OC use, and called for randomized trials to address these issues.

Women appear to be interested in reducing menstruation. When queried, 65% of Dutch women aged 25–34 preferred bleeding every 3 months or less often, and 31.1% desired no bleeding.⁹ Use of extended OC cycles to reduce cyclic symptoms with tolerable irregular bleeding has been shown to be effective.¹⁰ Extension of active pill use to produce cycles varying from 42 to 84 days has been studied in small populations, with different OC formulations, and with variable success regarding cycle control.^{8,11} Extending cyclical hormone pill use from 21 to 42 days reduced bleeding and need for hygiene products.¹¹ However, the number of spotting days among extended cycle subjects was similar to the 28-day cycle subjects, and spotting was still present at the year’s end.¹¹

Extended pill cycles imply that at least some scheduled withdrawal bleeding is necessary, rather than the complete omission of scheduled bleeding implied by continuous, uninterrupted, or daily OC use.

However, as with hormone replacement therapy, scheduled hormone withdrawal and bleeding may destabilize the endometrium, induce proliferation, and promote the persistence of irregular bleeding.¹² Histology from continuous hormone replacement users indicates greater endometrial suppression compared with cyclic hormone users.^{13,14} Irregular bleeding can trigger pill discontinuation and dissatisfaction, and fears of an increase in unexpected bleeding have been used to justify the promotion of regular monthly withdrawal bleeding as the optimal profile. But for many cyclic pill users, irregular bleeding events are quite common,^{15,16} and a continuous schedule with expected initial breakthrough bleeding might be tolerated to attain the goals of improved contraception and no bleeding.

Little work has been published regarding continuous or daily OC use. Coutinho et al compared 3726 continuous cycles with 3364 cyclic cycles in 900 women using a 50- μ g ethinyl estradiol/250- μ g levonorgestrel OC tablet administered intravaginally.¹⁷ Amenorrhea was rapidly induced, with 67.6% of continuous-use subjects reporting no bleeding by 3 months. This increased to 87.5% by the end of the year without an increase in OC discontinuation.¹⁷ In Italy, after surgical treatment for endometriosis, 90 women were randomized to either daily progestin only (cyproterone acetate 12.5 mg) or a continuous OC (20- μ g ethinyl estradiol/150- μ g desogestrel) for 6 months to prevent disease reoccurrence.¹⁸ At 6 months, the mean endometrial double layer thickness was 3.4 ± 0.9 mm, and amenorrhea was present in 46% of the continuous OC subjects.¹⁸ Overall satisfaction, pain symptom scores, and continuation were similar between groups, and the authors concluded continuous OC was best for long treatments to avoid the effects of estrogen deprivation.¹⁸ We initiated a year-long randomized trial, among women choosing contraception, to demonstrate that complete elimination of bleeding is possible with a low-dose monophasic OC preparation.

MATERIALS AND METHODS

The study was approved by the local Institutional Review Board, and women were recruited by flyer for contraception without an emphasis on the potential for bleeding reduction. Women were screened by telephone for exclusions before the clinic visit. The study was conducted from January 2000 to September 2001 at a University-affiliated, metropolitan, dedicated research clinic. Subjects were excluded for age less than 18 years

or greater than 45 years; standard contraindications to combined OC use; inability to speak or read English; contraceptive injection use in prior 6 months; current diagnosis of uterine infection, fibroid, or cervical dysplasia; hemoglobin less than 9.0 g/dL; or intention to become pregnant within 1 year. Written informed consent was obtained.

At the first in-person visit, subjects completed a self-administered demographic questionnaire, responded to standardized queries regarding medical and gynecologic history items, and underwent gynecologic examination, including a Papanicolaou smear. Subjects were measured for height, weight, blood pressure (BP), and capillary hemoglobin. Prior OC use history was collected, and a subject was classified as a new user if she had no prior OC use, as a restart if it had been greater than 30 days since her last OC use, or as a switcher if OC use was ongoing.

All subjects were given two 28-day packages of study medication (Alesse 20- μ g ethinyl estradiol/100- μ g levonorgestrel; Wyeth Laboratories, Philadelphia, PA) and told to take the spacer or hormone-free pills on days 22–28 of the cycle for a planned initial withdrawal bleed. The purpose of this first cycle (designated cycle 0) was to document that bleeding would occur with a pill-free week and as a run-in cycle to minimize study dropouts after randomization.¹⁹ Subjects recorded daily pill taking, and bleeding was scored (none, trace = no sanitary protection needed, mild = requiring one to two pads or tampons, or moderate = requiring more than two pads or tampons). At revisits, subjects returned the empty pill packs, and these were used to verify the diary reports. During cycle day 1 to 21 of the second pill package (designated study cycle 1), subjects returned for the enrollment and randomization visit. At this visit, subjects were not randomized for the following reasons: abnormal cervical cytology, absence of withdrawal bleeding, patient choice, and/or noncompliance defined as absent diary information or missing more than two consecutive or three total pills during days 1 to 21 of the first cycle.

An off-site institutional research pharmacy supplied the study medication, randomization schedule, and allocation verification. A computerized random number generator program with balanced blocks of ten (concealed from clinical study staff performing enrollment) was used to randomize subjects to treatment. Randomization was accomplished with the dispensing of identical sequentially numbered sealed brown bags containing study medication. The enrollment and randomization logs were closely monitored, and it was not possible to open a bag and then reassign it to another subject. There was no masking after randomization because the spacer pills are green in color unlike the pink active pills, and

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pill-taking instructions were different for the two study arms. Subjects randomized to the continuous arm were given 21-day pill packages without spacer pills and instructed to take only pink pills every day without interruption. Cyclic subjects were given 28-day pill packages and instructed to take the pills as packaged with pink hormone pills on days 1 to 21 and green spacer pills on days 22 to 28.

All subjects were asked to volunteer after randomization for a substudy involving a pelvic ultrasound and endometrial biopsy during cycles 1 and 9 to assess the endometrial changes with continuous compared with cyclic use. In addition, all subjects were told that if bleeding lasted longer than 10 days after cycle 3, they should return for pelvic examination, ultrasound, and endometrial biopsy. The pelvic ultrasound was performed by an outside facility. A hospital-based ultrasonographer, blinded to study assignment, used a 5.0-MHz vaginal probe to measure the double-layer endometrial thickness on sagittal view in the midbody of the uterus, assess endometrial stripe consistency, look for evidence of fibroids or submucous fibroids, and measure the size and number of ovarian follicles including the maximal follicle diameter. The endometrial biopsy was performed after the ultrasound on the same day if possible. Using a flexible plastic 4-mm collection device, the tissue was placed into formalin for routine hematoxylin and eosin staining. A single pathologist, blinded to study assignment, scored the specimen for adequacy and histology findings.

Every 3 months and at exit, subjects returned to the clinic for weight and BP measurement and to return their diaries. A urine pregnancy test was also performed if the subject was assigned to the continuous arm, if the subject was assigned to the monthly arm and reported absence of withdrawal bleeding, or if the subject was concerned about pregnancy. A standardized questionnaire was administered at each visit. Subjects were asked if they were worried about being pregnant, if the amount of bleeding had been less, equal to, or more than expected, how they were feeling in the past month (1 = poor to 5 = great), and to rate their level of satisfaction with their pill schedule using a 5-point scale (1 = not satisfied to 5 = better than other methods). Subjects were asked if they would recommend this birth control method to other women (1 = would absolutely not recommend to 5 = absolutely would recommend). Subjects were also asked, "Are there any symptoms you need to discuss?" and then the symptoms supplied by the woman were recorded. Specific symptoms (breast tenderness, nausea, and abdominal pain) were then queried for and quantified for their absence or frequency. All adverse events were recorded. Women quitting the study were queried

about their reason for discontinuation and the birth control method they planned to use after the study.

The primary outcome for the study was bleeding profile comparison between the OC schedules. Bleeding outcomes were evaluated using definitions adapted from the World Health Organization.²⁰ For each subject, bleeding patterns and pill-taking habits were analyzed both by 28-day and 84-day intervals with the first cycle (cycle 0) separate because this cycle was before randomization, and all subjects were scheduled to have withdrawal bleeding. Analyses included total number of bleeding days, number of spotting days, number of episodes of abnormal bleeding patterns,²⁰ and number of missed pills (a pill was considered "missed" even if it was taken the next day). Secondary outcomes for the study were patient satisfaction, study completion, and pregnancy.

Data were entered into a statistical spreadsheet. The study variables were entered as continuous variables or dichotomous variables as appropriate. Statistics were calculated using Splus (Unix 3.1; Mathsoft, Seattle, WA). For comparisons between the two study arms, significance values for continuous variables (eg, age, weight) were obtained by the Student *t* test. Significance values for counts (eg, number of bleeding days) were obtained by the Mann-Whitney test. Significance values for discrete variables were obtained by the Fisher exact test. Except where specifically stated otherwise, we used intention-to-treat analyses and included all collected data from all randomized subjects even if the subject exited early, had an endometrial biopsy, violated the protocol, or did not take study drug as directed.

Withdrawal bleeding for a typical combined OC user lasts on average 4 days.²¹ The goal of the study was to reduce bleeding days; hence, bleeding days were used to calculate the sample size of the study. It was assumed that during the same 84-day interval, 60% of the women using the 28-day regimen would bleed 12 days compared with only 20% of women using the continuous schedule. The minimum sample size to give the study adequate power (80%) with a two-tailed test to detect this 67% reduction would require 27 women in each arm (Epi Info 6; Centers for Disease Control and Prevention, Atlanta, GA). With an anticipated study dropout rate of 30%, we decided to enroll 80 women to obtain a complete year of data on 54 women.

RESULTS

Seventy-nine women were enrolled and randomized by August 2000. Data collection was completed by September 2001. Study completion rates by treatment arm and reasons for exclusion and dropout are listed in Figure 1.

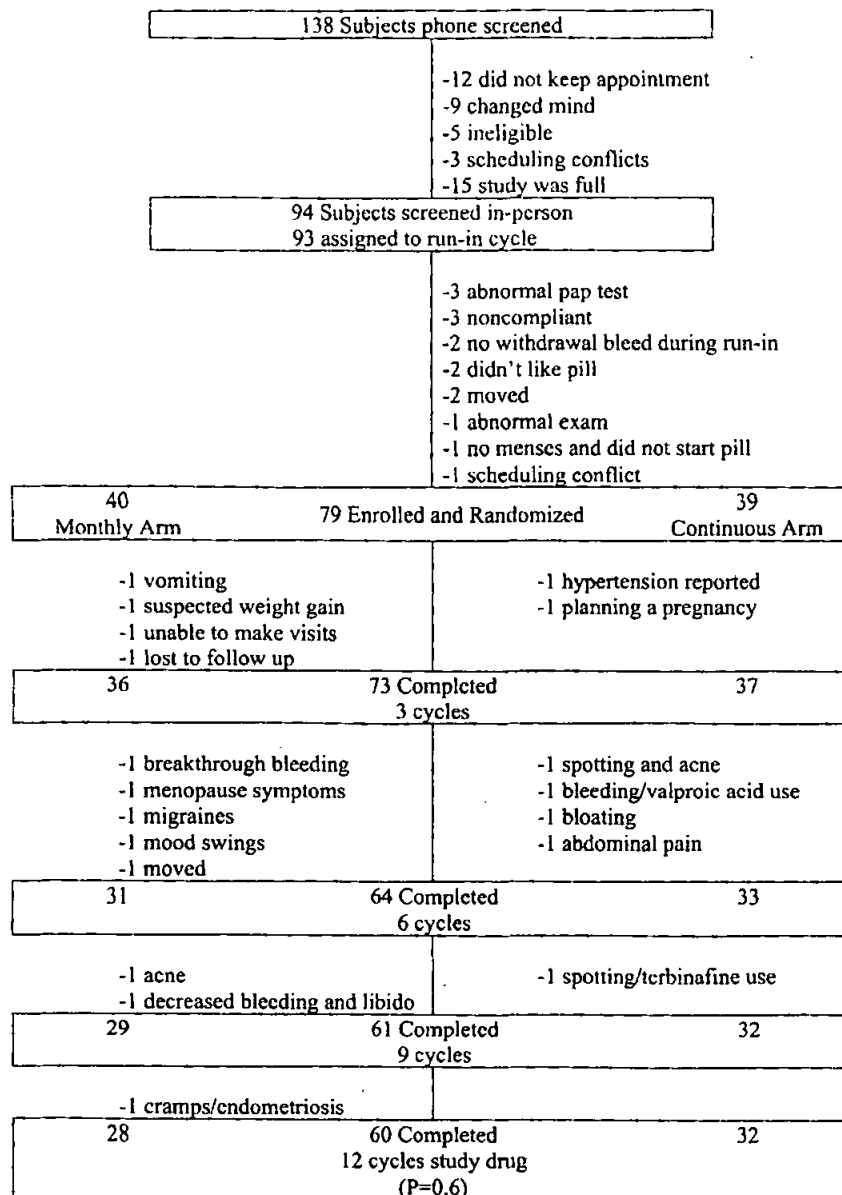


Figure 1. Subject flow chart.

Miller. Continuous Pill Use. *Obstet Gynecol* 2003.

Table 1 compares the enrollment demographics and baseline characteristics of the two study populations. There were no statistical differences in age, body mass index, gravidity, parity, partner status, ethnicity, smoking status, education, or prior OC use history between the two groups. Many subjects were using OC at the time of enrollment and subsequently switched to the study pill after the scheduled withdrawal or spacer week pill use (Table 1).

The median number of bleeding and spotting days per 84-day reference period for all subjects is shown in Table 2. Throughout the year, the continuous-use subjects

experienced fewer bleeding days without a statistically significant difference between the two groups in overall spotting days. However, when we restricted the analysis of spotting days to cycle days 1 to 21 (when the cyclic user is not supposed to have bleeding or spotting), we found that the median number of spotting days increased initially but then declined over time in the continuous users, whereas the cyclic users had little change in spotting over time (Table 2).

The percentage of women experiencing absence of bleeding days during a 28-day interval was significantly higher in the continuous arm during the entire study

Table 1. Enrollment Demographic Information

	28-day cycle (n = 40)	Continuous (n = 39)	P*
Age (y)	29.2 ± 7.6 [†]	27.4 ± 6.8 [†]	.29
Body mass index (kg/m ²)	25.4 ± 5.5 [†]	25.2 ± 5.4 [†]	.95
Nulligravidity (%)	55	74	.06
Nulliparity (%)	70	85	.11
Living with partner (%)	48	28	.10
White (%)	90	87	.74
Current smoker (%)	20	10	.35
Education (%)			1.0
High school or less	10	11	
College	73	74	
Graduate school	17	15	
Oral contraceptive (%)			.54
New user	5	2	
Restart pills [‡]	35	26	
Direct pill switch	60	72	

* Fisher exact test for discrete variables and Student *t* test for continuous variables.

[†]Standard deviation.

[‡]Greater than 30 days since birth control pill use.

after the run-in cycle (Figure 2). Using diary data and established criteria²⁰ for various bleeding patterns, the two study arms were compared between the first and last 84-day intervals of randomized study drug use (Table 3). Amenorrhea, absence of both bleeding and spotting, was reported by 16% of continuous-use subjects during cycles 1–3 and increased to 72% by cycles 10–12 (Table 3). All bleeding and spotting events were considered irregular bleeding in continuous OC subjects. These irregular bleeding events decreased over time but continued to occur in some subjects (Table 2). For example, during the last 84-day interval, nine (28%) of the 32 continuous-use subjects had an occasional spotting or bleeding day

and could not be considered to have amenorrhea. However, typically, this bleeding was very light. Only three of the 32 women using the continuous OC in the last 84 days had more than a single episode of bleeding, and only one subject reported a single day of bleeding heavy enough to require the use of more than two hygiene products. However, 12 (43%) of the 28 cyclic subjects reported bleeding heavy enough to necessitate the use of more than two hygiene products for at least 1 day in the last 84-day interval (data not shown).

There were seven women who exited early from the continuous arm (Figure 1), and although the reasons reported for exit were not primarily bleeding, analysis of their bleeding diary data revealed these women recorded more bleeding while on study than women completing the study. If all of these women had completed the study, then the total difference of bleeding days between study arms would have been less but would not invalidate the findings. Upon exiting the study, 16 (41%) of the 39 continuous OC users reported that the bleeding had been more than expected compared with seven of 40 (18%) cyclic arm subjects (*P* = .07).

In the first 84-day interval, nine (30%) cyclic women and five (15%) continuous-use women reported missing three or more pills (*P* = .26) compared with the last 84-day interval when seven (32%) cyclic and only two (7%) continuous-use subjects reported missing three or more pills (*P* = .07). Missed pills were analyzed using days 1 to 21 for the cyclic subjects and days 1 to 28 for the continuous-use subjects because many cyclic subjects refused to swallow the spacer pills or consistently missed spacer pills. An electronic diary study of OC compliance

Table 2. Reported Bleeding and Spotting Days per 84-Day Interval for All Subjects by Study Assignment

	28-day cycle* median (25%, 75%)	Continuous* median (25%, 75%)	P [†]
Total bleeding days			
Cycles 1–3	10.0 (8.0, 13.5)	3.0 (1.5, 9.0)	<.001
Cycles 4–6	9.0 (5.5, 13.0)	0.5 (0.0, 6.0)	<.001
Cycles 7–9	9.0 (6.5, 14.5)	0.0 (0.0, 1.0)	<.001
Cycles 10–12	9.0 (7.0, 14.0)	0.0 (0.0, 1.0)	<.001
Total spotting [‡] days			
Cycles 1–3	6.0 (3.5, 9.0)	9.0 (3.5, 17.0)	.09
Cycles 4–6	5.5 (4.0, 7.0)	7.5 (1.0, 20.0)	.31
Cycles 7–9	5.0 (4.0, 7.0)	7.0 (0.0, 14.0)	.88
Cycles 10–12	5.0 (3.0, 7.0)	1.5 (0.0, 11.5)	.32
Cycle days 1–21 spotting [‡] days			
Cycles 1–3	4.0 (1.0, 2.0)	6.0 (2.5, 12.5)	<.001
Cycles 4–6	3.0 (1.0, 4.0)	6.0 (.75, 14.0)	.02
Cycles 7–9	2.0 (1.0, 4.0)	3.0 (0.0, 11.0)	.24
Cycles 10–12	2.0 (0.0, 3.0)	0.5 (0.0, 8.5)	.82

*All days for subjects included, and *n* depends on study dropout (see Figure 1).

[†]Mann-Whitney test.

[‡]Spotting means visible blood but no hygiene product used.

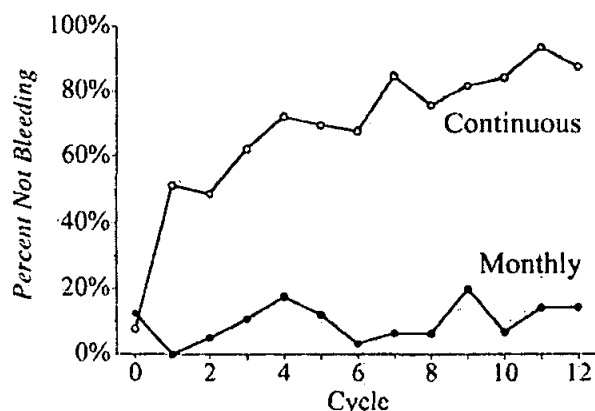


Figure 2. Percentage of all subjects reporting no bleeding days or hygiene product use by study cycle.

Miller. Continuous Pill Use. *Obstet Gynecol* 2003.

also excluded analysis of the spacer-pill week and made no comment regarding spacer-pill consumption data.²²

A total of 16 women agreed to a baseline pelvic ultrasound and endometrial biopsy with the expectation that these procedures would be repeated during cycle 9. This subset included nine women randomized to continuous use, and seven assigned to 28-day cycles. In addition, two continuous-use subjects with prolonged bleeding underwent these assessments during cycle 9. Endometrial thickness measurements were under 5 mm in all subjects during cycle 9 but did not correlate well with histologic diagnosis, and specimens read as proliferative could have been taken from a subject with an endometrial stripe under 3 mm in thickness. No histology result indicated hyperplasia or neoplasia at any time. During cycle 9, three (60%) of the five cyclic OC users undergoing biopsy had proliferative endometrium compared with seven (88%) of the eight continuous OC users with inactive or atrophic specimens. There were two women at baseline with uterine fibroids detected on ultrasound, both under 10 mm, but one was a 5-mm submucosal fibroid, which was later not seen at the cycle-9 ultrasound, and this subject still had some irregular bleeding during cycles 10–12. One of the subjects undergoing evaluation for prolonged bleeding had two (18 mm and 28 mm) fibroids located within the uterine wall.

There were three protocol violators. One continuous arm subject misunderstood the instructions to begin a new pill pack directly and allowed herself a pill-free week each cycle until the first revisit. This meant she did not have her first true continuous week until cycle 3. The second violator (also continuous arm) decided to use a higher-dose triphasic pill for two cycles to see if it would improve her libido. She took this higher-dose pill contin-

uously for cycles 9 to 10 with a reported improvement in her libido. She was the single continuous-use subject with proliferative histology on endometrial biopsy during cycle 9. When this deviation was discovered, she agreed to switch back to the study drug for the last two cycles of the study and again complained of decreased libido. The third violator was a cyclic arm subject who, during cycle 9, missed two consecutive pills and then stopped that pill pack, had a 7-day pill-free interval, and started a new pack after a total of 9 pill-free days. She did not become pregnant and completed the study.

Concern regarding a possible pregnancy was rare with only ten subjects reporting concern at revisit during the year. Five cyclic and four continuous-use subjects responded with "a little" concern, and a single cyclic subject reported "a lot" because of her absence of withdrawal bleeding during the spacer week. At no time did any subject report or have a positive pregnancy test.

Generally, weight, BP, and hemoglobin were not significantly different between study arms at baseline or exit (Table 4). Exceptions were hemoglobin at entry ($P = .04$) and systolic BP at exit ($P = .02$). Comparisons of an individual's change in these parameters from baseline to exit (data not shown) were not significantly different between study arms. Standardized questions at revisit and exit regarding estrogen-related symptoms found no difference in reported breast tenderness or nausea; both were infrequent complaints. However, abdominal pain was reported to have occurred at least once a month at

Table 3. Bleeding Patterns²⁰ Derived From Daily Diary From Subjects* Who Completed the First and Last 84-Day Intervals

	28-day cycle <i>n</i> (%)	Continuous <i>n</i> (%)
During cycles 1–3	(<i>n</i> = 36)	(<i>n</i> = 37)
Infrequent bleeding	0 (0)	25 (68)
Frequent bleeding	2 (5)	2 (5)
Intermenstrual bleeding	20 (56)	Not applicable
Prolonged bleeding	1 (3)	8 (22)
Amenorrhea	0 (0)	6 (16)
During cycles 10–12	(<i>n</i> = 28)	(<i>n</i> = 32)
Infrequent bleeding	3 (11)	28 (88)
Frequent bleeding	0 (0)	0 (0)
Intermenstrual bleeding	14 (50)	Not applicable
Prolonged bleeding	0 (0)	1 (3)
Amenorrhea	1 (4)	23 (72)

Infrequent bleeding = fewer than two episodes (one or more consecutive days = episode); frequent bleeding = more than four episodes; intermenstrual bleeding = at least 1 bleeding day during cycle days 1–21 in cyclic subjects; prolonged bleeding = one episode lasting more than 10 days; amenorrhea = neither bleeding nor spotting.

* Subjects may be listed twice (a woman with amenorrhea also meets the criteria for infrequent bleeding), and subjects with monthly bleeding or another bleeding pattern are not listed here.

Table 4. Safety Measurements

	28-day cycle	Continuous	P
Weight (lb)			
Baseline	153.1 ± 28.8	153.9 ± 34.8	.91
Exit all	155.7 ± 29.7	153.2 ± 36.8	.74
Exit completers	157.5 ± 32.8	156.3 ± 38.5	.89
Hemoglobin (g/dL)			
Baseline	12.7 ± 1.1	12.2 ± 1.0	.04
Exit completers	13.0 ± 1.1	13.1 ± 0.9	.58
Systolic pressure (mm Hg)			
Baseline	114.8 ± 10.4	113.6 ± 10.9	.64
Exit all	113.1 ± 11.9	108.9 ± 13.0	.14
Exit completers	115.6 ± 11.9	107.9 ± 13.2	.02
Diastolic pressure (mm Hg)			
Baseline	67.2 ± 9.5	67.5 ± 9.4	.88
Exit all	64.6 ± 4.4	64.6 ± 6.0	.98
Completers	65.5 ± 3.3	64.1 ± 5.4	.23

Data for all randomized subjects presented.

study exit by 72% of cyclic subjects and only 26% of continuous-use subjects ($P < .001$).

There were three serious adverse events, all in cyclic arm subjects who continued study drug use and went on to complete the study. None was considered to be related to study medication. The events were as follows: pyelonephritis, pneumonia, and a 30-year-old subject underwent emergent oophorectomy for pain from a benign dermoid tumor during study drug cycle 6. Adverse events were reported by 85% of cyclic and 87% of continuous-use subjects at least once during the study, and complaints causing study discontinuation are reported in Figure 1. Headaches were specifically recorded on the diary by eight women using cyclic OC, compared with only one continuous OC user. No continuous-use subject complained of mood changes, but three cyclic subjects reported this adverse event.

Method satisfaction scores using a 5-point scale (mean ± standard deviation) were slightly higher at exit for cyclic subjects (4.1 ± 1.3) compared with continuous-use subjects (3.8 ± 1.7), but this difference was not significant ($P = .09$). On a 5-point scale, continuous OC users (4.4 ± 1.0) were no more likely ($P = .83$) to recommend their method to other women than cyclic OC users (4.5 ± 1.0). Similarly, no difference between study arms was seen at exit in response to the general question "In the past month, how have you been feeling?" (cyclic 3.7 ± 1.0 , continuous 3.7 ± 1.0 , $P = .64$).

At exit, subjects completing the study were asked what type of birth control they planned to use. Twenty-five (78.1%) of the 32 continuous-use subjects planned to continue on daily active OC pill use without a period week, six (18.8%) planned to switch back to cyclic OC use (with three choosing a different OC formulation),

and only one subject planned to use no method. Of the 28 cyclic subjects completing the study, 19 (67.9%) planned to stay on a cyclic OC schedule, six (21.4%) planned to try continuous use, and three women chose no method at exit.

DISCUSSION

Continuous administration of a 20- μ g ethinyl estradiol monophasic OC was well tolerated and significantly reduced bleeding compared with cyclic use. Spotting days declined over time with continuous or daily use, and study dropout because of unacceptable bleeding was rare. By study cycle 2 (56 days of daily OC use), 49% of the continuous-use subjects reported no bleeding. This increased to 68% by cycle 6, and by year's end 88% of continuous-use subjects reported no bleeding (Figure 2). Complete amenorrhea (no bleeding or spotting) was reported by 23 (72%) of the 32 continuous-use subjects during the last 84-day time period.

This absence of bleeding was not associated with a fear of pregnancy. Only the cyclic subjects with a "silent" or missed menses expressed this concern. With the typical OC failure rate 50 times higher than the "perfect user" failure rate of 0.1%, eliminating the pill-free or spacer week might improve efficacy.²³ A previous continuous OC study detected a statistically significant reduction in pregnancies from four with cyclic use in 446 women to zero with daily or continuous OC administration in 454 women over 1 year.¹⁷ Our data suggest there was a small improvement in pill-taking compliance with daily consumption compared with cyclic use. However, we relied on a self-reported daily diary, and without electronic recording, it is likely subjects significantly under-reported missed pills.²² In our study, we extensively counseled pill taking as the key to preventing irregular bleeding, but we did not observe a correlation between missed pills and bleeding in our data.

It is likely a continuous OC schedule would induce greater ovarian suppression, and prevent ovulation, which continues in some women with cyclic OC use.^{24,25} Although shortening the pill-free week to 4 days with 24 days of active pill use produced greater ovarian suppression, it did not eliminate irregular bleeding, and often bleeding occurred beyond the pill-free interval.²⁶ Extreme individual variation is common when studying follicular and hormonal response to the OC, and this idiosyncratic response could explain how some women claim to miss only one pill and still conceive.²⁷

If continuous OC use is initiated properly and continued without interruption, then the risk of pregnancy should be very small. Even if a pregnancy were present, the modern OC dose is not a teratogen²⁸ and does not

increase the risk of fetal genital malformations.²⁹ Nonetheless, pregnancy testing for reassurance should be readily available during the first year of withdrawal bleeding suppression. Other contraceptive methods, such as the progestin-only injection or progestin-releasing intrauterine device, also alter menstrual bleeding (including significant rates of amenorrhea), but a monthly pregnancy test is not usually required. Although the OC efficacy depends on user compliance, it is still a decision under the woman's control and "get a pregnancy test if you are missing pills" is prudent advice.

Only a small percentage of our subjects underwent ultrasound and histology assessments, but the findings provide reassurance that there does not appear to be a "build up" within the uterus with continuous OC use. Instead, it appears the cyclic subjects with the scheduled withdrawal bleeding are the ones who experience a proliferation of the endometrium. It was considered novel and experimental to use continuous combined estrogen and progesterone during menopause years ago, but as early as 1981, there was histological documentation of endometrial atrophy and quiescence with daily progestin administration even after only 4 months of treatment.¹³ These same authors concluded that continuous replacement is "at least as effective as sequential therapy but without its inconvenience."¹³

Shedding the endometrium was always presumed to be essential to protecting the endometrium from cancer, but another study³⁰ of long-term estradiol replacement found the induction of withdrawal bleeding was not necessary to prevent hyperplasia. In fact, higher estrogen and progestin doses were needed to produce cyclic bleeding, and continuous combined therapy with low-dose estradiol induced amenorrhea while providing therapeutic estradiol levels.³⁰ In a recent study, cyclic progestin did not prevent all hyperplasia, whereas no case was found in continuous hormone replacement users.¹⁴ Continuous combined hormone replacement therapy has also been shown to increase compliance compared with cyclic use.³¹

Long-term cyclic OC use is very safe,³² and it is unlikely the loss of the pill-free week would greatly alter the safety, particularly if the total dose consumed is comparable to cyclic use. With 24 days of the 15- μ g ethinyl estradiol product, there were no significant pro-coagulant changes in homeostasis parameters.²⁶ However, in women using a 42-day cycle with a 30- μ g ethinyl estradiol preparation, there was a measurable trend after 1 year towards enhanced estrogenic metabolic effects.³³ To minimize potential additive estrogenic effects with the loss of the pill-free week, it may be reasonable to use only 20- μ g ethinyl estradiol OC products for daily use. The total ethinyl estradiol dose administered over 1 year

to the cyclic 30- μ g ethinyl estradiol OC user would be 8.2 mg, and this is more than the 7.3-mg ethinyl estradiol exposure if a 20- μ g ethinyl estradiol dose product were to be consumed daily. In addition, given the evidence regarding hormone replacement doses, it appears a lower estrogen dose would be most conducive to maintaining amenorrhea.³⁰

In summary, continuous OC use for 1 year was well tolerated without an increase in OC discontinuation and induced amenorrhea or infrequent bleeding in 88% of subjects with an initial increase but then an actual decrease in spotting days as the year progressed. Although our study is limited by numbers and duration of use, perhaps in time it may seem odd to cycle women on the OC, and "The difficulty is not so much in developing new ideas as in escaping from old ones" (John Maynard Keynes).

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(54) **ORAL CONTRACEPTIVES TO PREVENT
PREGNANCY AND DIMINISH
PREMENSTRUAL SYMPTOMATOLOGY**

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(57) **ABSTRACT**

This invention relates to a method of preventing pregnancy and treating PMS including PMDD. More particularly, the invention relates to a method, which involves administering one of several combination oral contraceptive regimens in combination with an antidepressant and a kit containing the same.

disorder. In these women, the diagnosis of Premenstrual Dysphoric Disorder (PMDD), which is defined in the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) can be applied. According to the DSM-IV, a woman with PMDD must have at least five premenstrual symptoms during the luteal phase, with at least one of the symptoms being an emotional or "core" symptom. The core symptoms must be irritability, anger, mood swings, tension or depression (and interfere with daily activities), and must be confirmed by a prospective daily rating for at least two cycles. Three to five percent of women with PMS report to have PMDD.

[0016] There is also a subgroup of women who experience severe PMS, which accounts for about 20% of the PMS population. These women experience severe emotional symptoms that do not fall under the strict criteria of PMDD as defined in DSM-IV but require medical attention.

[0017] Symptoms of PMDD may begin at any age after menarche, but the average age at onset appears to be around 26 years and several researchers found that symptoms, such as estrogen withdrawal symptoms, associated with the premenstrual phase gradually become worse, and perhaps more protracted, over time. It has been suggested that worsening could occur because of the recurring increases and decreases in ovarian hormones. This is supported by data from other cultures: when menstruation is infrequent, premenstrual symptoms are rare. It is also supported by data associating low parity with the risk of PMDD. Low parity yields a greater number of hormonal cycles, and, thus, a woman has more exposure to and withdrawal from massive amounts of progesterone. Further, several studies find lower rates of premenstrual symptoms among users of oral contraceptives, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD (Yonkers, K., *J. Clin. Psychiatry* 58(Suppl. 14):4-13 (1997)).

[0018] Suppression of ovulation has been an important rationale for the use of hormonal treatments for PMS. One method of inhibiting ovulation is by using oral contraceptives (OCs). Combination oral contraceptives inhibit ovulation by suppressing gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). To date, only two controlled studies of the oral contraceptive treatment of PMS have been published. The results indicate that combination oral contraceptives effectively reduce physical symptoms (especially breast pain and bloating), but the response on the relief of psychological symptoms has been less clear.

[0019] Therapeutic interventions for women who meet the criteria for PMDD include selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants and anxiolytics, as well as the antidepressant alprazolam (XANAX®). These interventions have demonstrated efficacy with minimal side effects. Recent investigations of SSRI have also demonstrated success at low doses.

[0020] Antidepressants that are active at serotonin receptors include clomipramine (ANAFRANIL®), fluoxetine (PROZAC®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®).

[0021] The only approved product today for the treatment of PMDD is the SSRI fluoxetine hydrochloride

(SARAFEM®). The effectiveness of fluoxetine for the treatment of PMDD was established in four randomized, placebo-controlled trials. Fluoxetine at a daily dose of either 20 mg or 60 mg proved to be superior to placebo in reducing symptoms (Steiner et al., *New Engl. J. Med.* 332:1529-34 (1995)). However, the combination of oral contraceptive and fluoxetine was not examined, as women who were taking oral contraceptives were excluded from the trial.

[0022] It is the object of the present invention to provide estrogen-progestin combinations and/or regimens for oral contraceptive use, including estrogen-progestin combinations and/or regimens that contain an antidepressant, to concurrently diminish or eliminate premenstrual symptoms (PMS) including PMDD. Two regimens are proposed, the so-called 28-day regimen and the 91-day regimen. The 28-day regimen will allow women the option of maintaining the customary 13 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. The 91-day regimen will allow women the option of maintaining only 4 menstrual cycles per year while diminishing or alleviating premenstrual symptoms (PMS) including PMDD. Thus, the 91-day regimen enhances compliance by involving fewer stop/start transitions per year and also results in less blood loss, and hypothetically, will diminish premenstrual symptoms, including PMDD. Having fewer menstrual intervals can also enhance lifestyles and convenience. This and other objects of the invention will become apparent to those skilled in the art from the following detailed description.

BRIEF SUMMARY OF THE INVENTION

[0023] This invention relates to female oral contraceptives that will prevent pregnancy and treat PMS including PMDD. This invention further relates to a method of preventing pregnancy and treating PMS including PMDD, by avoiding complete withdrawal of estrogen at the end of the treatment period, or between treatment periods, by administering oral contraceptives. Premenstrual symptoms are rare when menstruation is infrequent. Further, users of oral contraceptives have lower rates of premenstrual symptoms, again suggesting that briefer exposure to peaks and troughs of endogenous progesterone is protective against PMDD. More particularly, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens. Additionally, the invention relates to a method of preventing pregnancy, which involves administering one of two combination oral contraceptive regimens that contain an antidepressant.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The invention relates to oral contraceptives that will prevent pregnancy and diminish or eliminate PMS including PMDD. Methods of using these oral contraceptives to prevent pregnancy and diminish or eliminate PMS including PMDD are also provided. More particularly, the methods involve administering one of several combination oral contraceptive regimens. Importantly, these regimens do not contain pill-free or placebo intervals.

[0025] One embodiment of the invention is the so-called twenty-eight day regimen that allows women the option of maintaining 13 menstrual cycles per year. In accordance

[0032] In a preferred embodiment, women will be administered an oral contraceptive on days 1 through 84 of the menstrual cycle containing 150 μ g levonorgestrel and 30 μ g ethinyl estradiol, followed by a dosage form on days 85-91 of the cycle, which contains 30 μ g ethinyl estradiol and 20 mg fluoxetine hydrochloride. A typical administration schedule is illustrated in Table 4. Thus, in a 91-day regimen, there are only four treatment and menstrual cycles per year.

TABLE 4

Administration schedule for a 91-day regimen with an antidepressant		
Days	Hormone	Antidepressant
1-84	150 μ g levonorgestrel and 30 μ g ethinyl estradiol	none
85-91	30 μ g ethinyl estradiol	20 mg fluoxetine hydrochloride daily OR a one-time dose of 90 mg fluoxetine hydrochloride OR a once-weekly dose of 90 mg fluoxetine hydrochloride

[0033] The estrogens which may be employed as a component in the regimens of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens, including steroidal and nonsteroidal estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, ethynodiol diacetate, mestranol and quinestranol. Particularly of interest are 17 α -ethinyl estradiol and esters and ethers thereof. The preferred estrogen is 17 α -ethinyl estradiol. The natural estrogens may include, for example, conjugated equine estrogens, esterified estrogens, 17 β -estradiol, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate.

[0034] The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17 α -ethinyltestosterone and derivatives thereof, 17 α -ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fuingestanol acetate, medrogestone, norgestrienone, dimethiderome, ethisterone, cyproterone acetate, levonorgestrel, di-norgestrel, d-17 α -acetoxy-13 β -ethyl-17 α -ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene, desogestrel and norgestimate. The preferred progestin is levonorgestrel.

[0035] The weight ratio of the active ingredients, e.g., ethinyl estradiol and levonorgestrel, is at least 1:45 and preferably at least 1:50. The preferable amount of ethinyl estradiol is about 10-50 μ g and the preferable amount of levonorgestrel is about 0.15-1.5 mg. Other estrogens vary in potency from ethinyl estradiol. For example, 30 μ g of ethinyl estradiol is roughly equivalent to 60 μ g of mestranol or 2 g of 17 β -estradiol. Likewise, other progestins vary in potency from levonorgestrel. Thus, 1 mg of levonorgestrel is roughly equivalent to about 3.5 mg of norethindrone acetate, or 1 mg of desogestrel and 3-ketodesogestrel or about 0.7 mg of gestodene. The values given above are for ethinyl estradiol and levonorgestrel and if a different estrogen or progestin is employed, an adjustment in the amount based on

the relative potency should be made. The correlations in potency between the various estrogens and progestins are known. See for example European Patent Application No.0 253 607, which is hereby incorporated in its entirety by reference hereto.

[0036] The preferred antidepressant is fluoxetine hydrochloride although other antidepressants can be employed. For example, the antidepressants alprazolam (XANAX®), clomipramine (ANAFRANIL®), paroxetine (PAXIL®), sertraline (ZOLOFT®), nefazodone (SERZONE®), fenfluramine (PONDIMIN®) and venlafaxine (EFFEXOR®) can also be used. The daily amounts of these antidepressants can vary, depending on the antidepressant used, from 0.75 to 2 mg, 10 to 20 mg or 50 to 100 mg.

[0037] Each of the described regimens will prevent pregnancy and additionally diminish or eliminate debilitating premenstrual symptomatology.

[0038] Other useable estrogens include the esters of estradiol, estrone and ethinyl estradiol such as the acetate, sulfate, valtrate or benzoate, conjugated equine estrogens, agnostic anti-estrogens, and selective estrogen receptor modulators. The formulations of the invention may be administered orally, preferably in tablet form, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. The method of administration depends on the types of estrogens and progestins used in the formulation, as well as the amounts per unit dosage. Most estrogens are orally active and that route of administration is therefore preferred. Methods for transdermal administration including the associated methods for manufacturing such systems are well known in the art. In this connection, reference may be had to U.S. Pat. Nos. 4,752,478, 4,685,911, 4,438,139 and 4,291,014, which are hereby incorporated in their entirety by reference hereto.

[0039] Pharmaceutical formulations or preparations containing the formulations of the invention and a suitable carrier can be solid dosage forms which includes tablets, dragees, capsules, cachets, pellets, pills, powders or granules; topical dosage forms which include solutions, powders, fluid emulsions, fluid suspensions, semi-solids, ointments, pastes, creams, gels or jellies, foams and controlled release depot entities; transdermals, vaginal rings, buccal formulations; and parenteral dosage forms which includes solutions, suspensions, emulsions or dry powder comprising an effective amount of estrogen, progestin and antidepressant as taught in this invention.

[0040] It is known in the art that active ingredients can be contained in such formulations in addition to pharmaceutically acceptable diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers, humectants, moisturizers, solubilizers, preservatives and the like. The means and methods for administration are known in the art and an artisan can refer to various pharmacologic references for guidance. For example, "Modern Pharmaceutics", Banker & Rhodes, Marcel Dekker, Inc. (1979); "Goodman & Gilman's The Pharmaceutical Basis of Therapeutics", 6th Edition, MacMillan Publishing Co., New York (1980), or Remington's Pharmaceutical Sciences, Osol, A., ed., Mack Publishing Company, Easton, Pa. (1980) can be consulted.

[0041] Generally speaking, the formulations are prepared according to conventionally known procedures in accor-

ness symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe or extreme symptoms" (100 mm). The PMTS consists of a 36 item scale that will be completed by the patient and a 10-item scale completed by the blinded observer. Both scales rate premenstrual symptoms for a particular day; the total score can range from 0 (no symptoms) to 36 (all symptoms present and severe).

[0181] The secondary outcome will be defined as reduction in symptoms of PMS including PMDD as measured by the sub-score of somatic symptoms on VAS. The VAS will measure headache, bloating, pain and breast tenderness and weight gain symptoms. Patients will be prompted to rate how they feel each day using 100 mm scales in which the descriptors range from "no symptoms" (0 mm) to "severe symptoms" (100 mm). In addition to information recorded in paper diaries, a standardized questionnaire will be used to determine whether the patient had any side effects.

[0182] Statistical Analysis

[0183] For the primary analysis, the mean of the VAS scales will be derived to obtain a single VAS score, which evaluates composite psychological and symptomatic outcomes. Mean percent reduction from baseline at the luteal phase will be compared using an analysis of covariance (ANCOVA) approach that evaluates the effects of the treatment group, center and treatment-by-center interaction, after adjusting for the effect of the baseline VAS score. All statistical tests will be two-sided at the 0.05 level of significance. Pairwise comparisons will be made for each active treatment to placebo. Secondary analyses will include a set of statistical tests for the PMTS and 10-item blinded observer-based measures.

[0184] Application of the compounds, compositions and methods of the present invention for the medical or pharmaceutical uses described can be accomplished by any clinical, medical, and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. It will therefore be appreciated that the various embodiments which have been described above are intended to illustrate the invention and various changes and modifications can be made in the inventive method without departing from the spirit and scope thereof.

What is claimed is:

1. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 81-89 consecutive days, followed by administration of estrogen for a period of 2-10 consecutive days.

2. The method of claim 1, in which the daily amount of estrogen administered for 81-89 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

3. The method of claim 2, in which the daily amount of progestin administered for 81-89 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

4. The method of claim 3, wherein the combination of estrogen and progestin is administered for at least 84 consecutive days.

5. The method of claim 1, wherein the estrogen is administered for at least 7 consecutive days.

6. The method of claim 2, in which the estrogen is ethinyl estradiol.

7. The method of claim 3, in which the progestin is levonorgestrel.

8. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 21-26 consecutive days, followed by administration of estrogen for a period of 2-7 days.

9. The method of claim 8, in which the daily amount of estrogen administered for 21-26 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

10. The method of claim 9, in which the daily amount of progestin administered for 21-26 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

11. The method of claim 10, wherein the combination of estrogen and progestin is administered for at least 21 consecutive days.

12. The method of claim 8, wherein the estrogen is administered for at least 7 consecutive days.

13. The method of claim 9, in which the estrogen is ethinyl estradiol.

14. The method of claim 10, in which the progestin is levonorgestrel.

15. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 81-89 consecutive days, followed by administration of a combination of estrogen and an antidepressant for a period of 2-10 days.

16. The method of claim 15, in which the daily amount of estrogen administered for 81-89 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

17. The method of claim 16, in which the daily amount of progestin administered for 81-89 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

18. The method of claim 17, in which the daily amount of antidepressant administered for 2-10 consecutive days is equivalent to about 5-120 mg of fluoxetine hydrochloride.

19. The method of claim 15, wherein the combination of estrogen and progestin is administered for at least 84 consecutive days.

20. The method of claim 15, wherein the combination of estrogen and antidepressant is administered for at least 7 consecutive days.

21. The method of claim 16, in which the estrogen is ethinyl estradiol.

22. The method of claim 17, in which the progestin is levonorgestrel.

23. The method of claim 18, in which the antidepressant is fluoxetine hydrochloride.

24. The method of claim 15, wherein said combination of estrogen and antidepressant is administered in a single tablet.

25. A method of diminishing premenstrual symptoms in a female, comprising continuously administering a combination of estrogen and progestin for 21-26 consecutive days, followed by administration of a combination of estrogen and an antidepressant for a period of 2-7 days.

26. The method of claim 25, in which the daily amount of estrogen administered for 21-26 consecutive days is equivalent to about 5-50 μ g of ethinyl estradiol.

27. The method of claim 26, in which the daily amount of progestin administered for 21-26 consecutive days is equivalent to 0.05-1.5 mg of levonorgestrel.

28. The method of claim 27, in which the daily amount of antidepressant administered for 2-7 consecutive days is equivalent to about 5-120 mg of fluoxetine hydrochloride.

29. The method of claim 25, wherein the combination of estrogen and progestin is administered for at least 21 consecutive days.

30. The method of claim 25, wherein the combination of estrogen and antidepressant is administered for at least 7 consecutive days.

31. The method of claim 26, in which the estrogen is ethinyl estradiol.

32. The method of claim 27, in which the progestin is levonorgestrel.

33. The method of claim 28, in which the antidepressant is fluoxetine hydrochloride.

34. The method of claim 25, wherein said combination of estrogen and antidepressant is administered in a single tablet.

35. A kit to diminish premenstrual symptoms consisting of:

(a) tablets comprising estrogen and progestin; and

(b) tablets comprising estrogen.

36. The kit of claim 35, wherein said estrogen and progestin tablets include about 84 tablets and wherein said estrogen tablets include about 7 tablets.

37. The kit of claim 35, wherein said estrogen and progestin tablets include about 21 tablets and wherein said estrogen tablets include about 7 tablets.

38. The kit of claim 35, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

39. The kit of claim 38, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

40. The kit of claim 38, in which the estrogen is ethinyl estradiol.

41. The kit of claim 39, in which the progestin is levonorgestrel.

42. A kit to diminish premenstrual symptoms consisting of:

(a) tablets comprising estrogen and progestin; and

(b) tablets comprising estrogen and an antidepressant.

43. The kit of claim 42, wherein said estrogen and progestin tablets include about 84 tablets and wherein said estrogen and antidepressant tablets include about 7 tablets.

44. The kit of claim 42, wherein said estrogen and progestin tablets include about 21 tablets and wherein said estrogen and antidepressant tablets include about 7 tablets.

45. The kit of claim 42, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

46. The kit of claim 45, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

47. The kit of claim 46, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

48. The kit of claim 46, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of fluoxetine hydrochloride.

49. The kit of claim 45, in which the estrogen is ethinyl estradiol.

50. The kit of claim 46, in which the progestin is levonorgestrel.

51. The kit of claim 47, in which the antidepressant is fluoxetine hydrochloride.

52. A preparation for diminishing premenstrual symptoms in a female comprising about 84 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of estrogen.

53. The preparation of claim 52, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

54. The preparation of claim 53, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

55. The preparation of claim 53, in which the estrogen is ethinyl estradiol.

56. The preparation of claim 54, in which the progestin is levonorgestrel.

57. A preparation for diminishing premenstrual symptoms in a female comprising about 21 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of estrogen.

58. The preparation of claim 57, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

59. The preparation of claim 58, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

60. The preparation of claim 58, in which the estrogen is ethinyl estradiol.

61. The preparation of claim 59, in which the progestin is levonorgestrel.

62. A preparation for diminishing premenstrual symptoms in a female comprising about 84 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of a combination of estrogen and an antidepressant.

63. The preparation of claim 62, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

64. The preparation of claim 63, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

65. The preparation of claim 64, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

66. The preparation of claim 64, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of fluoxetine hydrochloride.

67. The preparation of claim 63, in which the estrogen is ethinyl estradiol.

68. The preparation of claim 64, in which the progestin is levonorgestrel.

69. The preparation of claim 65, in which the antidepressant is fluoxetine hydrochloride.

70. A preparation for diminishing premenstrual symptoms in a female comprising about 21 tablets consisting of a combination of estrogen and progestin and about 7 tablets consisting of a combination of estrogen and an antidepressant.

71. The preparation of claim 70, in which the amount of estrogen in the tablets is equivalent to about 5-50 μg of ethinyl estradiol.

72. The preparation of claim 71, in which the amount of progestin in the tablets is equivalent to 0.05-1.5 mg of levonorgestrel.

73. The preparation of claim 72, in which the amount of antidepressant in the tablets is equivalent to about 5-120 mg of fluoxetine hydrochloride.

74. The preparation of claim 72, in which the amount of antidepressant in the tablets is equivalent to about 90 mg of fluoxetine hydrochloride.

75. The preparation of claim 71, in which the estrogen is ethinyl estradiol.

76. The preparation of claim 72, in which the progestin is levonorgestrel.

77. The preparation of claim 73, in which the antidepressant is fluoxetine hydrochloride.

78. The method of claim 5, whereby a one-time dose of an antidepressant is administered in combination with the estrogen.

79. The method of claim 78, in which the antidepressant is fluoxetine hydrochloride.

80. The method of claim 79, in which the amount of fluoxetine hydrochloride administered is about 90 mg.

81. The method of claim 12, whereby a one-time dose of an antidepressant is administered in combination with the estrogen.

82. The method of claim 81, in which the antidepressant is fluoxetine hydrochloride.

83. The method of claim 82, in which the amount of fluoxetine hydrochloride administered is about 90 mg.

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(54) Title: METHODS OF HORMONAL TREATMENT UTILIZING CONTRACEPTIVE REGIMENS WITH CONTINUOUS ESTROGEN ADMINISTRATION

(57) Abstract: The present invention provides contraceptive regimens in which a female is administered a combined dosage form of estrogen and progestin followed by a period of administration of estrogen. The disclosed contraceptive regimens can be administered to a female as a method of providing non-contraceptive benefits.

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METHODS OF HORMONAL TREATMENT UTILIZING
CONTRACEPTIVE REGIMENS WITH CONTINUOUS ESTROGEN
ADMINISTRATION

BACKGROUND OF THE INVENTION

Field of the Invention

[0001] The present invention relates to methods of hormonal treatment that utilize contraceptive regimens involving administration of estrogen and progestin, followed by administration of estrogen.

Related Art

[0002] The human menstrual cycle involves a repetitive sequence of hormonal changes that result in episodic uterine bleeding. Normally, each menstrual cycle has a mean interval of about 21 to about 35 days, conventionally beginning with the first day of menstrual flow and ending on the day before the next onset of bleeding. Duration of the menstrual flow is usually about 2 to about 6 days with loss of about 20 to about 60 ml of blood.

[0003] The menstrual cycle is divided into follicular and luteal phases, each corresponding to changes occurring in the ovary. These phases may also be described as proliferative or secretory, corresponding to changes observed in the uterine endometrium. Variations in the length of the cycle are usually due to alterations in the follicular phase, because the luteal phase length remains relatively constant at about 12 to about 16 days.

[0004] During the follicular phase, several primary follicles are recruited for further growth and development. Granulosa cells in primary follicles possess follicle stimulating hormone (FSH) and estradiol receptors. Upon FSH stimulation, granulosa cells produce aromatase. This enzyme converts the androgens androstenedione and testosterone, made in response to luteinizing hormone (LH) by thecal cells, to estrone and estradiol, respectively. Granulosa cells respond to estradiol by undergoing mitosis to increase the

TABLE 1
Combinations of Progestin and Estrogen

Progestin	Norethindrone		Estrogen	EE Equivalent		P/E Ratio
	Dose (mg)	Dose (mg)		Dose (mg)	Dose (mg)	
Norethynodrel	9.85	9.85	Mestranol	0.150	0.105	93.810
	5.00	5.00		0.075	0.053	95.238
	2.50	2.50		0.036	0.025	99.206
	2.50	2.50		0.100	0.070	35.714
Norethindrone	10.00	10.00	Mestranol	0.060	0.042	238.095
	2.00	2.00		0.100	0.070	28.571
	1.00	1.00		0.050	0.035	28.571
	1.00	1.00		0.080	0.056	17.857
Norethindrone	1.00	1.00	Ethinyl estradiol (EE)	0.050	0.050	20.000
	1.00	1.00		0.035	0.035	28.571
	0.50	0.50		0.035	0.035	14.286
	0.40	0.40		0.035	0.035	11.429
Norethindrone acetate	2.50	2.50	EE	0.050	0.050	50.000
	1.00	1.00		0.050	0.050	20.000
	0.60	0.60		0.030	0.030	20.000
	1.50	1.50		0.030	0.030	50.000
	1.00	1.00		0.020	0.020	50.000
Ethinodiol diacetate	1.00	1.00	Mestranol	0.100	0.070	14.286
Ethinodiol diacetate	1.00	1.00	EE	0.050	0.050	20.000
Ethinodiol diacetate	1.00	1.00		0.035	0.035	28.571
dl-Norgestrel	0.50	0.75	EE	0.050	0.050	10.000
	0.30	0.45		0.030	0.030	10.000
Levonorgestrel	0.10	0.35	EE	0.020	0.020	5.000
	0.15	0.52		0.030	0.030	5.000

Equivalencies

50 mg Mestranol = approx. 35 mg Ethinyl estradiol (EE)

0.1 mg dl-Norgestrel = approx. 0.15 mg Norethindrone

[0158] Each block in Table 1 describes a specific combination of progestin and estrogen, e.g., norethynodrel and mestranol, and within each block older combinations are listed first, with successively newer combinations following.

[0159] Suitable progestins for use in the present invention include, but are not limited to, natural and synthetic compounds having progestational activity, such as, for example, progesterone, chlormadinone acetate, norethindrone, cyproterone acetate, norethindrone acetate, desogestrel, levonorgestrel,

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WHAT IS CLAIMED IS:

1. A method of reducing breakthrough bleeding in a female in need thereof, the method comprising administering to the female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

2. A method of reducing breakthrough bleeding in a female in need thereof, the method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

3. The method of claim 1, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

4. The method of claim 3, wherein the estrogen that is administered for a period of about 2 to about 10 days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

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5. The method of claim 4, wherein the estrogen that is administered for a period of about 2 to about 10 days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

6. The method of claim 4, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

7. The method of claim 4, wherein said female is a perimenopausal female.

8. A method of inducing regular, predictable withdrawal bleeding in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

9. A method of inducing regular, predictable withdrawal bleeding in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

10. The method of claim 8, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive

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days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

11. The method of claim 10, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

12. The method of claim 10, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

13. The method of claim 11, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

14. The method of claim 10, wherein said female is a perimenopausal female.

15. A method of reducing frequency of onset of a menstrual cycle or withdrawal bleed in a female in need of delayed or reduced menstruation, said method comprising administering to said female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

16. A method of reducing frequency of onset of a menstrual cycle or withdrawal bleed in a female in need of delayed or reduced menstruation, said method comprising administering to said female a combination of estrogen and progestin for a period of more than about 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10

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consecutive days, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

17. The method of claim 15, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

18. The method of claim 17, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

19. The method of claim 18, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

20. The method of claim 18, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

21. The method of claim 18, wherein said female is a perimenopausal female.

22. A method of inducing amenorrhea in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days,

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followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

23. A method of inducing amenorrhea in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

24. The method of claim 22, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

25. The method of claim 24, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

26. The method of claim 25, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

27. The method of claim 25, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

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28. A method of minimizing uterine bleeding in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

29. A method of minimizing uterine bleeding in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

30. The method of claim 28, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

31. The method of claim 30, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

32. The method of claim 30, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

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33. The method of claim 32, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

34. The method of claim 28, wherein said female is a perimenopausal female.

35. The method of claim 28, wherein said female exhibits abnormal uterine bleeding.

36. The method of claim 35, wherein said abnormal uterine bleeding is menorrhagia.

37. A method of treating an ovarian cyst, uterine leiomyoma (fibroid tumor), or treating Polycystic Ovarian Disease in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

38. The method of claim 37, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

39. The method of claim 37, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is

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administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

40. The method of claim 39, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

41. The method of claim 40, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

42. The method of claim 41, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

43. The method of claim 40, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

44. The method of claim 40, wherein said female is a perimenopausal female.

45. The method of claim 40, wherein said female is a menopausal female.

46. A method of treating hirsutism in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

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47. The method of claim 46, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

48. The method of claim 46, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

49. The method of claim 48, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol.

50. The method of claim 49, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

51. The method of claim 50, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

52. The method of claim 49, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

53. The method of claim 49, wherein said female is a perimenopausal female.

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54. The method of claim 49, wherein said female is a menopausal female.

55. A method of decreasing risk of iron deficiency anemia in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

56. A method of decreasing risk of iron deficiency anemia in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days., wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

57. The method of claim 55, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

58. The method of claim 57, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

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59. The method of claim 57, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

60. The method of claim 59, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

61. The method of claim 58, wherein said female is a perimenopausal female.

62. A method of treating a menstrual disorder in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of about 81 to about 110 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days;

wherein said menstrual disorder is selected from the group consisting of irregular menstrual cycles, dysmenorrhea, and mittelschmerz.

63. A method of treating a menstrual disorder in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days,

wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly; and

wherein said menstrual disorder is selected from the group consisting of irregular menstrual cycles, dysmenorrhea, and mittelschmerz.

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64. The method of claim 62, wherein the estrogen that is administered in combination with progestin for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of about 81 to about 110 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

65. The method of claim 64, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

66. The method of claim 64, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

67. The method of claim 66, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

68. The method of claim 65, wherein said female is a perimenopausal female.

69. The method of claim 62, wherein said menstrual disorder is dysmenorrhea.

70. A method of treating acne in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by

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administration of estrogen for a period of about 2 to about 10 consecutive days.

71. The method of claim 70, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

72. The method of claim 70, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

73. The method of claim 72, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

74. The method of claim 72, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 10 μ g to about 30 μ g of ethinyl estradiol.

75. The method of claim 74, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

76. The method of claim 75, wherein said female is a perimenopausal female.

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77. The method of claim 75, wherein said female is a menopausal female.

78. A method of treating endometriosis in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

79. The method of claim 78, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

80. The method of claim 78, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

81. The method of claim 80, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

82. The method of claim 81, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

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83. The method of claim 82, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

84. The method of claim 81, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

85. The method of claim 81, wherein said female is a perimenopausal female.

86. The method of claim 81, wherein said female is a menopausal female.

87. A method of reducing the risk of endometrial cancer in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

88. The method of claim 87, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

89. The method of claim 87, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

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90. The method of claim 89, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

91. The method of claim 90, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

92. The method of claim 91, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

93. The method of claim 90, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

94. The method of claim 90, wherein said female is a perimenopausal female.

95. The method of claim 90, wherein said female is a menopausal female.

96. A method of reducing the risk of ovarian cancer in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

97. The method of claim 96, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to

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about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

98. The method of claim 96, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

99. The method of claim 98, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

100. The method of claim 99, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

101. The method of claim 100, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

102. The method of claim 99, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

103. The method of claim 99, wherein said female is a perimenopausal female.

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104. The method of claim 99, wherein said female is a menopausal female.

105. A method of treating benign breast disease in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 50 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

106. The method of claim 105, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

107. The method of claim 105, wherein the estrogen that is administered in combination with progestin for a period of more than 50 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 50 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

108. The method of claim 107, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

109. The method of claim 108, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

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110. The method of claim 109, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

111. The method of claim 108, wherein the combination of estrogen and progestin is administered for a period of more than a year.

112. The method of claim 108, wherein said female is a peri-menopausal female.

113. The method of claim 108, wherein said female is a menopausal female.

114. A method of reducing the risk of colorectal cancer in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

115. The method of claim 114, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

116. The method of claim 114, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

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117. The method of claim 116, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

118. The method of claim 117, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

119. The method of claim 118, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

120. The method of claim 117, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

121. The method of claim 117, wherein said female is a perimenopausal female.

122. The method of claim 117, wherein said female is a menopausal female.

123. A method of treating an infection in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

124. The method of claim 123, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to

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about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

125. The method of claim 123, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

126. The method of claim 125, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

127. The method of claim 126, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

128. The method of claim 127, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

129. The method of claim 126, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

130. The method of claim 126, wherein said female is a perimenopausal female.

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131. The method of claim 126, wherein said female is a menopausal female.

132. The method of claim 123, wherein said infection is Pelvic Inflammatory Disease.

133. The method of claim 123, wherein said infection is a sexually transmitted disease.

134. A method of treating temporomandibular disorder in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

135. The method of claim 134, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

136. The method of claim 134, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

137. The method of claim 136, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

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138. The method of claim 137, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

139. The method of claim 138, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

140. The method of claim 137, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

141. The method of claim 137, wherein said female is a perimenopausal female.

142. The method of claim 137, wherein said female is a menopausal female.

143. A method of treating a catamenial symptom in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

144. The method of claim 143, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

145. The method of claim 143, wherein the estrogen that is administered in combination with progestin for a period of more than 20

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consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

146. The method of claim 145, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol.

147. The method of claim 146, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

148. The method of claim 147, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

149. The method of claim 146, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

150. The method of claim 146, wherein said female is a perimenopausal female.

151. The method of claim 143, wherein said catamenial symptom is a symptom associated with asthma, rheumatoid arthritis, seizure disorders, multiple sclerosis, diabetes, or migraine headache.

152. A method of treating non-menstrual related headache in a female in need thereof, said method comprising administering to the female a

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combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

153. The method of claim 152, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

154. The method of claim 152, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

155. The method of claim 154, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

156. The method of claim 155, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

157. The method of claim 156, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

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158. The method of claim 155, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

159. The method of claim 155, wherein said female is a perimenopausal female.

160. The method of claim 155, wherein said female is a menopausal female.

161. A method of treating non-menstrual related nausea in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

162. The method of claim 161, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

163. The method of claim 161, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

164. The method of claim 163, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is

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administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

165. The method of claim 164, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

166. The method of claim 165, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

167. The method of claim 164, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

168. The method of claim 164, wherein said female is a perimenopausal female.

169. A method of treating non-menstrual related depression in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

170. The method of claim 169, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

171. The method of claim 169, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to

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about 50 µg of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

172. The method of claim 171, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol.

173. The method of claim 172, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

174. The method of claim 173, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

175. The method of claim 172, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

176. The method of claim 172, wherein said female is a perimenopausal female.

177. The method of claim 172, wherein said female is a menopausal female.

178. A method of increasing contraceptive effectiveness in a higher weight female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 50 consecutive days, followed by administration of estrogen for a period of about

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2 to about 10 consecutive days; wherein said higher weight female weighs about 70 kg or more.

179. The method of claim 178, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

180. The method of claim 178, wherein the estrogen that is administered in combination with progestin for a period of more than 50 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 50 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

181. The method of claim 180, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

182. The method of claim 181, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

183. The method of claim 182, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

184. The method of claim 181, wherein said female is a perimenopausal female.

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185. A method of increasing fertility in a female in need thereof, the method comprising:

(i) administration to the female of a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days;

(ii) discontinuation of administration of the combination of estrogen and progestin for the period of more than 20 consecutive days and of estrogen for the period of about 2 to about 10 consecutive days; and

(iii) optional administration to the female of an ovulation-inducing agent during the discontinuation of administration of the combination of estrogen and progestin for the period of more than 20 consecutive days and of estrogen for the period of about 2 to about 10 consecutive days;

wherein fertility in the female is increased.

186. The method of claim 185, wherein the ovulation-inducing agent is administered to the female during the discontinuation of administration in (ii) of the combination of estrogen and progestin for the period of more than 20 consecutive days, and of the estrogen for the period of about 2 to about 10 consecutive days.

187. The method of claim 186, wherein the ovulation-inducing agent is clomiphene citrate or menotropins.

188. A method of treating or diminishing a perimenopausal symptom in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

189. The method of claim 188, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to

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about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

190. The method of claim 188, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

191. The method of claim 190, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

192. The method of claim 191, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

193. The method of claim 192, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

194. The method of claim 191, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

195. The method of claim 191, wherein said perimenopausal symptom is selected from the group consisting of hot flushes, dryness of the vagina, and osteoporosis.

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196. A method for treating a condition resulting from menopausal estrogen decline in a menopausal female, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

197. The method of claim 196, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

198. The method of claim 196, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

199. The method of claim 198, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

200. The method of claim 199, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

201. The method of claim 200, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

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202. The method of claim 199, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

203. A method of treating hypoestrogenism in a female in need thereof, said method comprising administering to said female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

204. The method of claim 203, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

205. The method of claim 203, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

206. The method of claim 205, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

207. The method of claim 206, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

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208. The method of claim 207, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

209. The method of claim 206, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

210. The method of claim 206, wherein said female is a perimenopausal female.

211. The method of claim 206, wherein said female is a menopausal female.

212. A method of treating a menopausal disorder in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

213. The method of claim 212, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

214. The method of claim 212, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

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215. The method of claim 214, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

216. The method of claim 215, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

217. The method of claim 216, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

218. The method of claim 215, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

219. A method of maintaining bone density or preventing loss of bone density in a female in need thereof, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days, followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

220. The method of claim 219, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

221. The method of claim 219, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to

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about 50 µg of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

222. The method of claim 221, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 µg to about 50 µg of ethinyl estradiol.

223. The method of claim 222, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

224. The method of claim 223, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

225. The method of claim 222, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

226. The method of claim 222, wherein said female is a perimenopausal female.

227. The method of claim 222, wherein said female is a menopausal female.

228. A method of treating a female in need of hormone replacement therapy, said method comprising administering to the female a combination of estrogen and progestin for a period of more than 20 consecutive days,

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followed by administration of estrogen for a period of about 2 to about 10 consecutive days.

229. The method of claim 228, wherein an antidepressant is administered (i) in combination with the estrogen for the period of about 2 to about 10 consecutive days, (ii) continuously, (iii) intermittently, (iv) one time, or (v) once weekly.

230. The method of claim 228, wherein the estrogen that is administered in combination with progestin for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol, and the progestin that is administered in combination with estrogen for a period of more than 20 consecutive days is administered in a daily amount equivalent to about 0.05 mg to about 1.5 mg of levonorgestrel.

231. The method of claim 230, wherein the estrogen that is administered for a period of about 2 to about 10 consecutive days is administered in a daily amount equivalent to about 5 μ g to about 50 μ g of ethinyl estradiol.

232. The method of claim 231, wherein the combination of estrogen and progestin is administered for a period of about 60 to about 110 consecutive days.

233. The method of claim 232, wherein the combination of estrogen and progestin is administered for a period of about 81 to about 89 consecutive days.

234. The method of claim 231, wherein the combination of estrogen and progestin is administered for a period of about 21 to about 26 consecutive days.

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235. The method of claim 25, wherein said female is a perimenopausal female.

236. The method of claim 31, wherein said female is a menopausal female.

237. The method of claim 164, wherein said female is a menopausal female.