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Determination of estradiol and progesterone content in capsules and creams from compounding pharmacies

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Abstract

Objectives: To analytically characterize the doses of estradiol and progesterone found in compounded combined forms of oral capsule and transdermal cream formulations, and determine the consistency of the hormone formulations within a batch.

Methods: Prescriptions for combined estradiol/progesterone capsules (0.5 and 100 mg, respectively) and creams (0.5 and 100 mg/g, respectively) were sent to 15 custom-compounding pharmacies. Estradiol and progesterone levels were measured by radioimmunoassays. Hormone levels were measured in 2 capsules and 2 creams from each pharmacy; 10 capsules from 3 pharmacies; and top/middle/bottom layer of cream containers to assess consistency. The magnitude and sources of variation for the measurements were examined by analysis of variance models.

Results: Thirteen pharmacies filled the prescriptions. Measured estradiol levels were 0.365 to 0.551 mg for capsules and 0.433 to 0.55 mg/g for creams, and progesterone levels were 90.8 to 135 mg for capsules and 93 to 118 mg/g for creams. Greater variations in estradiol levels were observed between pharmacies for estradiol in capsules than in creams; however, measured estradiol levels within pharmacies were more consistent in the capsules than the creams. Similar results were obtained for progesterone levels.

Conclusion: The variations in estradiol and progesterone levels observed in compounded hormone therapy formulations justify concerns regarding risks as a result of variability, which have been outlined by The North American Menopause Society, the American College of Obstetricians and Gynecologists, and the US Food and Drug Administration (FDA) in their statements regarding compounded hormone use. These data support the need for an US FDA-approved bioidentical hormone therapy.

Key Words: Compounded pharmacies – Estradiol – Hormone therapy – Menopause – Progesterone.

Video Summary: Supplemental Digital Content 1, http://links.lww.com/MENO/A425.

Many postmenopausal women are treated with hormone therapy (HT) in an attempt to alleviate symptoms of menopause, primarily hot flushes, night sweats, and vaginal atrophy, and to prevent osteoporosis.[1] The postmenopausal period has been considered an endocrine-deficient state, and HT can help restore the premenopausal endocrine milieu.[2] Estrogen is the principal hormone used to treat postmenopausal symptoms.[1] A variety of estrogenic preparations are available, including the natural endogenous estrogen, 17β-estradiol.[1] To prevent endometrial hyperplasia from the effects of exogenous estrogens in women with a uterus, a progestogen is used either continuously combined or sequentially with the estrogens.[3] The progestogens available for therapeutic use are synthetic progestogens (progestins), and also natural progestogen (progesterone).[1]

A high demand for HT-containing natural hormones is shown by the estimated annual prescriptions of up to 21 million products containing natural progesterone, representing the most prescribed form of HT in the United States.[4] Because there was no single US Food and Drug Administration (FDA)-approved formulation containing both estradiol and progesterone before 2018, most of these (up to 18 million

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prescriptions) were for non-US FDA-approved compounded HT.[4] In October, 2018, the US FDA approved the first oral softgel capsule containing 1 mg of estradiol and 100 mg of progesterone, as Bijuva (TherapeuticsMD, Boca Raton, FL).

While combining both estradiol and progesterone in a single dosage form may be considered ideal for therapeutic reasons and convenient for patients, the difference in chemical structure between the compounds and their poor aqueous solubility present challenges in producing formulations with the appropriate bioavailability. Yet, many compounding pharmacies manufacture such combination products without the quality checks required of US FDA-approved drugs. Compounding pharmacies are monitored primarily by local state pharmacy boards with the US FDA having limited oversight. Some compounded drugs, including those used for HT, have been suspected of contamination and potency issues.[5,6] US FDA surveys conducted in 2001 and 2006, to examine the identity, strength, quality, and purity of compounding products, found that 33% of the compounded products tested failed mostly due to superpotency or subpotency (measured concentration was more than 10% from expected concentration), with potency ranging from 67.5% to 268.4%.[7,8] This deviation from targeted drug concentrations in compounded products is in stark contrast to the typical failure rate of <2% seen in routine US FDA testing of commercially manufactured products.[6] Thus, products from compounding pharmacies are approximately 10 times more likely to deviate significantly from the stated dose.

The purpose of this study was to analytically characterize the doses of estradiol and progesterone found in compounded combined forms of oral capsules and transdermal cream formulations, and determine the consistency of the formulations within a batch.

METHODS

Sample acquisition

Prescriptions for estradiol combined with progesterone in capsules (0.5 and 100 mg, respectively) and creams (0.5 and 100 mg/g, respectively) were sent to 15 compounding pharmacies selected from 81 pharmacies located in the United States and listed on the internet. The 15 pharmacies were selected using a random number generator. Each pharmacy had to be able to supply both products to be included in the study. If a pharmacy could not fill both (capsule and cream) prescriptions for any reason, the next number on the random generator list was used until 15 pharmacies were identified.

The pharmacies sent the products via FedEx or UPS courier using overnight delivery. Upon arrival, the packages were not opened, but were inspected for damage, which was documented. Each inspected package was then placed inside another overnight shipping package and sent directly to the testing laboratory, Reproductive Endocrine Research Laboratory, Keck School of Medicine of USC (Los Angeles, CA) by courier.

At the testing laboratory, the package was inspected for damage, and photographs were taken of the outer and inner package, pharmacy package, actual product, and product label. A checklist was completed to document the chain of product custody. The capsules from each pharmacy came in a vial, and ranged from 30 to 100 capsules per vial. Cream prescriptions were sent in containers or prefilled, metered syringe. The products were kept in the original package and stored in a cool room with no sunlight exposure. Estradiol and progesterone analyses of the products were carried out within 2 weeks from the time they were received.

Measurements of estradiol and progesterone in capsules and creams

Levels of estradiol and progesterone were measured in two randomly selected capsules and two randomly selected cream samples from each pharmacy. To study the variation in hormone level preparations within a pharmacy, 10 capsules were randomly selected from three pharmacies. Homogeneity of hormone levels was also measured in creams. Using a metered syringe, aliquots were taken from the top, middle, and bottom layers of cream containers from three pharmacies. Concentrations of estradiol and progesterone were determined by radioimmunoassay (RIA).

Estradiol

Each capsule was first thoroughly dissolved in chloroform to a total volume of 20 mL in conical-bottom plastic tubes (50-mL size). Similarly, 1 g of each cream was dissolved in acetone to a total volume of 20 mL. Because 0.5 mg of estradiol was supposed to be in each capsule and each gram of cream, the estradiol concentration was expected to be 0.5 mg/20 mL = 25 μg/mL (basic stock solution). Five serial dilutions (to 2,500 ng/mL, 250 ng/mL, 25 ng/mL, 1,250 pg/mL, and 250 pg/mL) were made (with ethanol for the first three dilutions and buffer for the last two dilutions) of the basic stock solution in 20-mL glass vials.

The last concentration (fifth dilution, 250 pg/mL) of the samples was then diluted serially (1:1) in assay buffer, and 0.2-mL aliquots from concentrations expected to be 62.5 pg/mL, 15.6 pg/mL, and 3.9 pg/mL were used for an in-house RIA. The RIA utilized a specific antiserum against estradiol, in conjunction with an iodinated estradiol derivative. After incubation overnight (16-18 h), the antibody-bound estradiol was separated from unbound estradiol using a second antibody. After centrifugation, the radioactivity in the pellet was counted. The estradiol concentrations of the samples were back-calculated from the estradiol standard curve (range 0.5-125 pg/mL) using a computer program. The assay sensitivity was 2 pg/mL. The interassay coefficients of variation (CVs) were 10%, 13%, and 12% at estradiol concentrations of 30 pg/mL, 88 pg/mL, and 262 pg/mL, respectively.

Progesterone

Each capsule was first thoroughly dissolved in chloroform to a total volume of 40 mL in conical-bottom plastic tubes. Similarly, 1 g of each cream was dissolved in acetone to a total volume of 40 mL. Assuming that 100 mg of progesterone was

TABLE 1. *Estradiol concentration in capsules (0.5 mg) and creams (0.5 mg/g) from 13 pharmacies*

Pharmacy number	Capsules (mg)					Creams (mg/g)				
	Capsule 1	Capsule 2	Mean ± SD	% CV	% Diff observed vs expected	Cream 1	Cream 2	Mean ± SD	% CV	% Diff observed vs expected
1	0.452	0.472	0.462 ± 0.014	3.06	−7.6	0.460	0.481	0.471 ± 0.015	3.16	−5.8
2	0.489	0.511	0.500 ± 0.016	3.11	0	0.490	0.510	0.500 ± 0.014	2.83	0
3	0.506	0.503	0.504 ± 0.002	0.42	0.8	0.491	0.522	0.506 ± 0.022	4.33	1.2
4	0.451	0.446	0.448 ± 0.004	0.79	−10.4	0.477	0.464	0.470 ± 0.009	1.95	−6.0
5	0.497	0.500	0.498 ± 0.002	0.43	−0.4	0.484	0.455	0.469 ± 0.021	4.37	−6.2
6	0.394	0.410	0.402 ± 0.011	2.81	−19.6	0.433	0.457	0.445 ± 0.017	3.81	−11
7	0.486	0.504	0.495 ± 0.013	2.57	−1.0	0.478	0.512	0.495 ± 0.024	4.86	−1
8	0.502	0.493	0.497 ± 0.006	1.28	−0.6	0.477	0.504	0.490 ± 0.019	3.89	−2
9	0.365	0.376	0.370 ± 0.008	2.10	−26	0.476	0.522	0.499 ± 0.033	6.52	−0.2
10	0.479	0.487	0.483 ± 0.006	1.17	−3.4	0.521	0.481	0.501 ± 0.028	5.65	0.2
11	0.488	0.496	0.492 ± 0.006	1.15	−1.6	0.471	0.496	0.483 ± 0.018	3.66	−3.4
12	0.532	0.519	0.525 ± 0.009	1.75	5.0	0.464	0.529	0.496 ± 0.046	9.26	−0.8
13	0.486	0.481	0.483 ± 0.004	0.73	−3.4	0.534	0.480	0.507 ± 0.038	7.53	1.4

CV, coefficient of variation; Diff, difference; SD, standard deviation.

contained in each capsule and 1 g of cream, the concentration would be expected to be 100 mg/40 mL = 2,500 μg/mL (basic stock solution). Five serial dilutions (to 250 μg/mL, 25 μg/mL, 2,500 ng/mL, 250 ng/mL, and 25 ng/mL) were made of the basic stock solution similar to the estradiol sample preparation procedure.

The last concentration (fifth dilution, 25 ng/mL) was then diluted serially (1:1) in buffer, and 0.05-mL aliquots from concentrations expected to be 12.5 ng/mL, 3.13 ng/mL, and 0.95 ng/mL were taken for RIA, using a commercial kit (Cisbio Bioassays, Codolet, France). The assay was carried out in progesterone antibody-coated tubes in conjunction with an iodinated progesterone derivative. After a 2-hour incubation at 37°C, the contents of the tubes were aspirated. The tubes were washed and then the radioactivity was counted in a gamma counter. The progesterone concentrations of the samples were back-calculated from the progesterone standard curve (range 0.12-36 ng/mL) using a computer program. Assay sensitivity was 0.12 ng/mL. The interassay CVs were 5%, 12%, and 11% at progesterone concentrations of 18.1 ng/mL, 77.0 ng/mL, and 137 ng/mL, respectively.

Statistical analysis

Estradiol and progesterone measurements were summarized within and between pharmacies by mean, standard deviation (SD), CVs, and percent difference between expected and observed concentrations. The magnitude and sources of variation for measurements of estradiol and progesterone within and across pharmacies were examined by fitting nested random-effects analysis of variance (ANOVA) models. Statistical analyses were performed using SAS/STAT V9.2 software.

RESULTS

Thirteen of the 15 pharmacies to which prescriptions were sent filled the prescriptions. Examination of each package received from the pharmacy showed no damage to the outer and inner portions of the packages, or to the pharmacy package. All products were labeled properly.

For the capsules (Table 1), samples from 11 pharmacies had estradiol mean measurements within 10% of the label claim (ranging from 0.448 to 0.525 mg), whereas the other 2 pharmacies had mean estradiol measurements of 0.370 mg (26% below label) and 0.402 mg (20% below label). For the cream samples, estradiol levels from 12 pharmacies were within 10% of the label claim; one pharmacy had an estradiol measurement 11% below label (mean of 0.445 mg/g). Estradiol sample measurements from the same pharmacy differed by as much as 0.065 mg (13%).

Estradiol in capsules differed significantly among the pharmacies ($P < 0.0001$), and pharmacy accounted for 96.0% of the total variance. In contrast, estradiol measurements in the creams did not differ significantly among the pharmacies ($P = 0.46$), and only 2.7% of the total variance was due to pharmacy.

Mean progesterone concentrations measured in the capsules (Table 2) ranged from 91.4 to 105 mg (±10% of the label claim) for 11 pharmacies; the other 2 pharmacies had mean progesterone levels of 116 mg (16% above label) and 131 mg (31% above label). For the creams, progesterone levels were within 10% of the label claim in 12 pharmacies; one pharmacy had mean levels of 112 mg/g for creams (12% above label). Progesterone sample measurements from a single pharmacy differed by as much as 13.2 mg (13%).

Progesterone in capsules also differed significantly among the pharmacies ($P < 0.0001$), and pharmacy accounted for 86.6% of the total variation, with 13.1% of the variation due to differences in duplicate measurements within pharmacy. However, progesterone in creams was not significantly different among pharmacies ($P = 0.081$). Pharmacy differences accounted for 38.4% of the total variation, whereas 61.6% of the variation was due to within-pharmacy differences.

The within-pharmacy variation of estradiol and progesterone measurements was further tested in 10 capsules each from three pharmacies (Table 3). The within-pharmacy CV for estradiol in 10 capsules was similar to the CV observed when measuring two samples from one pharmacy (pharmacy 1). However, the within-pharmacy CVs were higher for the other

TABLE 2. *Progesterone concentrations in capsules (100 mg) and creams (100 mg/g) from 13 pharmacies*

Pharmacy number	Capsules (mg)					Creams (mg/g)				
	Capsule 1	Capsule 2	Mean ± SD	% CV	% Diff observed vs expected	Cream 1	Cream 2	Mean ± SD	% CV	% Diff observed vs expected
1	121	112	116 ± 6.4	5.46	16	97.8	104	101 ± 4.4	4.35	1
2	91.6	95	93.3 ± 2.4	2.58	−7	93	96.5	94.7 ± 2.5	2.61	−5
3	135	128	131 ± 4.9	3.76	31	104	100.5	102 ± 2.5	2.42	2
4	96	97.2	96.6 ± 0.8	0.88	−3	107	104	105 ± 2.1	2.01	5
5	96.4	94	95.2 ± 1.7	1.78	−5	107	118	112 ± 7.8	6.91	12
6	94	99.2	96.6 ± 3.7	3.81	−3	94	98	96.0 ± 2.8	2.95	−4
7	105	103	104 ± 1.4	1.36	4	96	99.6	97.8 ± 2.5	2.60	−2
8	105	105	105 ± 0	0	5	107	102.2	105 ± 3.4	3.24	5
9	104	99	101 ± 3.5	3.48	1	104	109	106 ± 3.5	3.32	6
10	102	98	100 ± 2.8	2.83	0	95	106	100 ± 7.8	7.74	0
11	96.8	110	103 ± 9.3	9.03	3	103	96	98.0 ± 2.8	2.89	−2
12	90.8	92	91.4 ± 0.8	0.93	−9	100	96.2	98.1 ± 2.7	2.74	−2
13	100	105	102 ± 3.5	3.45	2	98	110	104 ± 8.5	8.16	4

CV, coefficient of variation; Diff, difference; SD, standard deviation.

2 pharmacies (pharmacies 5 and 12). Overall, estradiol levels differed significantly among the pharmacies ($P = 0.034$), with pharmacy accounting for 22.2% of the total variation. For progesterone, all three pharmacies had higher CVs with 10 capsules than the two samples measured from each pharmacy. Progesterone levels also differed among the pharmacies, with 23.8% of the total variation due to pharmacy.

When homogeneity of the creams (Table 4) across three pharmacies was measured by comparing hormone levels from the top, middle, and bottom layers, estradiol levels were slightly higher in samples taken from the top and middle versus bottom (mean 0.52, 0.51, and 0.487 mg/g, respectively). Progesterone levels were higher in the top and middle layers than in the bottom layer (mean 106, 109, and 103 mg/g, respectively). The sample sizes were too small for statistical testing of differences between the three locations.

DISCUSSION

Estradiol and progesterone are highly potent molecules with low aqueous solubility. These characteristics make them a challenge to formulate and to formulate consistently. Specifically, progesterone is a Biopharmaceutical Classification System Class II drug (poorly soluble-highly permeable); thus its bioavailability is associated with its solvation rate and therefore greatly impacted by how it is formulated.[9]

Testing of steroid hormone products from compounding pharmacies shows that the dose of the product received may be different from the actual prescribed dose.[6] When we evaluated estradiol and progesterone doses in compounded, combined estradiol and progesterone formulations and determined the consistency of the formulations across pharmacies and within a batch, variability was observed. Our results showed that for the estradiol in capsules, greater variation was evident between pharmacy-compounded capsules (range of mean 0.370-0.525 mg) than in creams (range of mean 0.445-0.507 mg/g). However, within pharmacies, there was more consistency in the capsules (range of % CV 2.66-4.56) than in the creams (range of % CV 2.98-9.17). Similarly, the range of means for progesterone in capsules was 91.4 to 131 mg, and 94.7 to 112 mg/g in creams between pharmacies. However, the within-pharmacy consistency was similar between capsules (range of % CV 6.05-7.27) and creams (range of % CV 2.11-7.20).

In general, the safety of compounded products has been a government concern for the last two decades, including concerns over potency (too weak or too strong), purity (could

TABLE 3. *Estradiol and progesterone concentrations in 10 capsules from three pharmacies*

Capsules/pharmacy	Estradiol (mg)			Progesterone (mg)		
	1	5	12	1	5	12
1	0.518	0.478	0.491	121	99	111
2	0.497	0.464	0.507	110	97.8	120
3	0.483	0.500	0.481	98	101	111
4	0.484	0.472	0.551	120	103	105
5	0.503	0.494	0.529	109	110	106
6	0.483	0.460	0.492	110	109	109
7	0.488	0.483	0.482	103	115	125
8	0.516	0.515	0.500	99	99	109
9	0.507	0.440	0.500	116	96	110
10	0.498	0.480	0.480	111	108	121
Mean ± SD	0.498 ± 0.013	0.479 ± 0.021	0.501 ± 0.023	110 ± 8.0	104 ± 6.3	113 ± 6.8
% CV	2.66	4.48	4.56	7.27	6.09	6.05

CV, coefficient of variation; SD, standard deviation.

TABLE 4. *Estradiol and progesterone concentrations in top, middle and bottom portions of creams from different pharmacies*

	Estradiol (mg/g)			Progesterone (mg/g)		
Cream/pharmacy	1	5	12	1	5	12
Top	0.55	0.48	0.53	109	108	101
Middle	0.49	0.54	0.50	115	113	98
Bottom	0.46	0.49	0.51	99.6	104	97
Mean ± SD	0.50 ± 0.05	0.50 ± 0.03	0.51 ± 0.02	108 ± 7.76	108 ± 4.5	98.7 ± 2.1
% CV	9.17	6.39	2.98	7.20	4.16	2.11

CV, coefficient of variation; SD, standard deviation.

contain chemicals that could be harmful), and contamination (bacteria, fungus, or virus).[7,10] Compounding drugs are not subject to the same US FDA regulations or oversight as other noncompounding products, and are not routinely tested by any regulatory agency for quality, purity, or potency.[10] Thus, some compounded products, including HT, may be associated with increased risks.[11]

Because dose, duration, and ratio of estrogens to progesterone are well known to affect endometrial protection, ensuring the accuracy of the dose of the estrogen and progestogen components used for HT is critical.[10] Thus, improperly formulated HT combinations could have serious health consequences, such as endometrial cancer, in users. However, because compounded drugs are not systematically studied, limited safety reports are available. A few publications reported cases of endometrial hyperplasia and endometrial cancer with the use of custom-compounded estradiol and progesterone products prescribed to relieve menopausal symptoms.[12-15] For example, one of the women diagnosed with atypical endometrial hyperplasia used a 2% compounded topical estradiol gel and a 6% compounded topical progesterone gel daily.[14,15] A North American Menopause Society (NAMS) survey of postmenopausal women with menopausal symptoms also reported an increased risk of endometrial cancer and suggested an increase in vaginal bleeding with compounded HT compared with US FDA-approved HT.[16]

While estradiol and progesterone are administered in supraphysiological doses, we believe that a relatively small reduction in dose (eg, 20%) would impact the endometrial protection in some women. For example, some women may be high metabolizers of steroid hormones, leading to decreased circulating progesterone levels, which may be insufficient for endometrial protection. Small changes in the ratio of estradiol to progesterone could also potentially have a negative impact on the endometrium with long-term exposure. In addition, because we studied only 13 pharmacies, it is possible that greater reductions in dose may have been found in compounded drugs from other pharmacies. A reduced dose in creams would be especially important in women who do not apply the cream as instructed, as the entire dose would not be applied.

This study has a few limitations, including the small number of pharmacies queried, how the pharmacies were chosen (internet only), and the small number of samples tested; therefore, our results may not accurately represent products coming from all US compounding pharmacies. Another limitation of the study is the inherent variability of the RIA method.

CONCLUSIONS

The variation in estradiol and progesterone levels observed in compounded HT formulations justify concerns regarding risks as a result of variability, that have been outlined by NAMS,[1] the American College of Obstetricians and Gynecologists,[17] and US FDA[18] in their statements regarding compounded hormone use. These data support the need to develop an US FDA-approved bioidentical HT, for women who prefer bioidentical hormones, including the up to 3 million women using unregulated, compounded HT annually in the United States.[19]

REFERENCES

1. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2017;24:728-753.
2. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 2010;95:s1-s66.
3. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. *Cochrane Database Syst Rev* 2012;CD000402.
4. TherapeuticsMD. TXMD Overview; 2017. Available at: https://ir.therapeuticsmd.com/static-files/c2e7f9d1-d150-4b4d-8703-e4f5c362169c. Accessed January 7, 2018.
5. Mahaguna V, McDermott JM, Zhang F, Ochoa F. Investigation of product quality between extemporaneously compounded progesterone vaginal suppositories and an approved progesterone vaginal gel. *Drug Dev Ind Pharm* 2004;30:1069-1078.
6. US Food and Drug Administration. Report: Limited FDA Survey of Compounded Drug Products. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm155725.htm. Accessed June 22, 2018.
7. Congressional Research Service. Compounded Drugs. Available at: https://fas.org/sgp/crs/misc/R43082.pdf. Accessed October 10, 2018.
8. Fairleigh Dickinson University School of Pharmacy & Health Sciences. MI3 Alert: Medical Innovation Impact Index. Available at: https://view2.fdu.edu/Report-8_v2099d.pdf?id=18361. Accessed October 10, 2018.
9. Savla R, Browne J, Plassat V, Wasan KM, Wasan EK. Review and analysis of FDA approved drugs using lipid-based formulations. *Drug Dev Ind Pharm* 2017;43:1743-1758.
10. Bhavnani BR, Stanczyk FZ. Misconception and concerns about bioidentical hormones used for custom-compounded hormone therapy. *J Clin Endocrinol Metab* 2012;97:756-759.
11. Pinkerton JV, Pickar JH. Update on medical and regulatory issues pertaining to compounded and FDA-approved drugs, including hormone therapy. *Menopause* 2016;23:215-223.

12. Eden JA, Hacker NF, Fortune M. Three cases of endometrial cancer associated with ''bioidentical'' hormone replacement therapy. *Med J Aust* 2007;187:244-245.
13. Davis R, Batur P, Thacker HL. Risks and effectiveness of compounded bioidentical hormone therapy: a case series. *J Womens Health (Larchmt)* 2014;23:642-648.
14. Dezman VL, Gersak MZ, Gersak K. Two cases of atypical endometrial hyperplasia associated with ''bioidentical'' hormone replacement therapy: IGCS-0084 Uterine Cancer, including Sarcoma. *Int J Gynecol Cancer* 2015;25 (Suppl 1):71.
15. Gersak K, Gersak B, Lucija VD. Postmenopausal overtreatment with ''bioidentical'' hormones in custom-compounded preparations: a case report. *Climacteric* 2014;17:58-59.
16. Gass ML, Stuenkel CA, Utian WH, et al. Use of compounded hormone therapy in the United States: report of The North American Menopause Society Survey. *Menopause* 2015;22:1276-1284.
17. American College of Obstetricians and Gynecologists. Management of menopausal symptoms. Practice Bulletin No. 141. *Obstet Gynecol* 2014;123:202-216.
18. US Food and Drug Administration. Compounding and the FDA: Questions and Answers. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm339764.htm. Accessed January 8, 2016.
19. Pinkerton J, Santoro N. Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women. *Menopause* 2015;22:926-936.