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Opioid Endocrinopathy in Women Consuming Prescribed Sustained-Action Opioids for Control of Nonmalignant Pain

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Abstract: Hypogonadotrophic hypogonadism is characteristically induced in men by intrathecal, transdermal, or sustained-action opioids. Although women receiving intrathecal opioids have similar changes, often accompanied by amenorrhea, hypogonadotrophic hypogonadism has not been documented in women receiving sustained-action, transdermal, or oral opioids. Dehydroepiandrosterone sulfate deficiency, indicating adrenal inhibition, is present in most men and women chronically consuming sustained-action oral or transdermal opioids. We recorded menstrual histories and measured gonadotrophin, androgen, and estradiol levels in 47 women ages 30 to 75 years who were consuming sustained-action oral or transdermal opioids for control of nonmalignant pain and in 68 non–opioid-consuming control subjects. Testosterone, estradiol, and dehydroepiandrosterone sulfate values were 48% to 57% lower in opioid-consuming women with intact ovarian tissue than in control subjects ($P < .01$–$.05$). Luteinizing hormone and follicle-stimulating hormone values averaged 30% lower in premenopausal and 70% lower in postmenopausal opioid consumers ($P < .001$). Among oophorectomized women not consuming estrogen, free testosterone levels were 39% lower in opioid consumers ($P < .05$), indicating impaired adrenal androgen production. Additional lowering of free testosterone levels was associated independently with oral estrogen replacement and low body mass index. Menses had often ceased soon after beginning sustained-action opioid therapy. Our observations document hypogonadotrophic hypogonadism plus decreased adrenal androgen production in most women consuming sustained-action oral or transdermal opioids.

***Perspective:** These observations demonstrate profound inhibition of ovarian sex hormone and adrenal androgen production among women chronically consuming sustained-action opioids. Related consequences include altered menstrual flow, probable reduced fertility, and possible contributions to opioid-associated depression, osteoporosis, and hyperalgesia. Measurements of bone density, estradiol, and free testosterone may guide appropriate therapy.*

***Key words:** Hypogonadism, opioids, pain/drug therapy, DHEAS, testosterone, estradiol, gonadotrophins, amenorrhea.*

Opioids inhibit the production of multiple hypothalamic, pituitary, gonadal, and adrenal hormones. Most of these changes have been well documented in men, who characteristically have development of lowered blood levels of cortisol, testosterone, and gonadotrophins within 1 to 4 hours after acute opioid administration,[16] with levels returning to normal during the next 24 hours.[53] This opioid endocrinopathy (OE) is usually present during the use of either illicit[16] or prescribed opioids administered by intravenous,[17,22,36,37] oral,[11-13,16,38,53] transdermal,[12,13,32] or intrathecal[1,18,34] routes. The opioid-associated hypogonadotrophic hypogonadism in men usually includes symptomatic testosterone deficiency,[11-13,38] a syndrome that has been labeled opioid-induced androgen deficiency (OPIAD).[12] Evidence of opioid-induced inhibition of adrenal function includes inhibited cortisol production immediately after acute intravenous opioid administration[17,54] and soon after oral opioid ingestion,[53] impaired cortisol metabolism during intrathecal[1] or oral[16] therapy, and subnormal levels of dehydroepiandrosterone sulfate (DHEAS), the major adrenal androgen, in a majority of both men and women

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during chronic use of sustained-action oral or transdermal opioids.[12,16]

Evidence of OE in female opioid consumers has been reported infrequently, even though amenorrhea, hypomenorrhea, sexual dysfunction, fatigue, and depression are prominent in many female heroin addicts, including those receiving once daily methadone therapy[2,16,42] and in most women receiving continuous intrathecal opioids for treatment of nonmalignant pain.[1,18,34] After being given 5 mg of morphine intravenously, women have rapid development of lower leuteinizing hormone (LH) levels.[22,36] These findings have led to diagnoses of hypogonadotrophic hypogonadism in these populations[1,2,16,18] and demonstration of decreased estriol and DHEAS levels in pregnant heroin addicts receiving low-dose daily methadone maintenance.[2,16] Testosterone levels reported in female opioid consumers are apparently, however, limited to the data of Cofrancesco et al,[8] who reported 16% lower total testosterone values ($P < .03$) among the 31 women on methadone maintenance within in a group of 196 subjects at high risk for HIV disease. Other details of these methadone consumers which might have modified testosterone levels including age, body mass index (BMI), smoking status, and methadone doses were not reported. Hypogonadotrophic hypogonadism has not been formally reported in women receiving the commonly prescribed sustained-action oral or transdermal opioid dosage forms.

After noting sexual dysfunction, fatigue, depression, premature menopause and osteoporosis in many women who were consuming prescribed sustained-action oral or transdermal opioids, we elected to examine gonadotrophin, sex hormone, and DHEAS levels in women with retained ovarian tissue who were chronically consuming sustained-action opioids and not receiving hormonal therapy, opioid consumers with prior oophorectomy who either were or were not using oral estrogen replacement (OER), and community-dwelling non–opioid-consuming control subjects.

Methods

Outpatient noninstitutionalized women, aged 30 to 75 years, who were chronically consuming sustained-action oral or transdermal opioids for control of nonmalignant pain, as well as non–opioid-consuming control subjects, were recruited for interview and hormone analyses by public solicitation and from the private practices of physicians in Redding, a community of 80,000 residents in rural Far Northern California, between October 2003 and May 2006. Both opioid consumers and control subjects were excluded with conditions recognized to potentially modify sex hormone or gonadotrophin levels, including pregnancy or breast feeding within the past year, and consumption of anticonvulsant medications, systemic or inhaled corticosteroids, testosterone, estrogen, progesterone, or DHEA within the past 2 years. Women were included, however, with prior bilateral oophorectomy whether or not they were consuming oral estrogen replacement. All control subjects meeting these criteria were included in analyses, and each received $20.00 for her participation in addition to copies of her hormone evaluations.

All opioid consumers had used either multiple daily doses of a sustained-action oral opioids totaling at least 20 mg of methadone, 30 mg of oxycodone, or 30 mg of morphine sulfate, or continuous transdermal fentanyl at 25 μg/h for at least 1 month (median duration, 2 years; range, 1 month–14 years), each of these minimums representing 20 "methadone equivalents."[11,30] Most opioid consumers were being treated for chronic back pain, often having failed 1 or more spinal operations, 3 had complex regional pain syndrome type 1, and 4 had chronic abdominal or pelvic pain. Ninety percent of subjects were Caucasian. All opioid consumers and control subjects were outpatients who were in stable health, without apparent acute or chronic infectious, inflammatory, malignant, or endocrine disease, except for menopause. None had been hospitalized within the preceding 6 months.

Data recorded including height, weight, age, menstrual history, and current medications, plus tobacco and alcohol use. Total testosterone (TT), estradiol (E2), LH, follicle-stimulating hormone (FSH), sex-hormone binding globulin (SHBG), and DHEAS were measured in a single blood sample, obtained without regard to time of day, by immunochemiluminometric assay (IMCS) by our reference laboratory, Lab Corp, Burlington, NC (www.labcorp.com). Free testosterone (FT) values were calculated from TT and SHBG levels by the method recommended by Vermeulen et al.[51] More precise techniques for determining testosterone values in women were not available from our reference laboratory. Dates of hormone analyses were not coordinated with menses because menstrual flow could rarely be predicted in opioid consumers. Daily opioid doses were converted into "methadone equivalent" doses for examination of relations between opioid doses and other variables.

Control women were classified as postmenopausal if they had undergone bilateral oophorectomy or if they fulfilled 2 of these 3 criteria: E2 level <30 mg/mL, LH >26 mIU/mL, and FSH >22 mIU/mL. The profound suppression of LH and FSH in opioid consumers of all ages precluded the use of gonadotrophin values in determining their menopausal status, and no completely satisfactory definition of the postmenopausal state among them could be established. Opioid consumers were classified as postmenopausal if they had undergone bilateral oophorectomy or if they fulfilled 2 of the following 3 criteria: E2 level <30 pg/mL, irregular or absent menses for 6 months, and prominent night sweats or hot flashes. Included among the weaknesses of this definition is the potential for return of fertility should opioid consumption be discontinued.

In computing average hormone values for categories of subjects, values which were below the lower detection limited of our reference laboratory were included as 67% of this lower detection limit, an assumption made among opioid consumers for DHEAS (<15 μg/dL) in 16 women, TT (<10 ng/dL) in 4 women, and E2 (<10 pg/mL) in 7 women. Among control subjects, the assumption

Table 1. Subject Use of Sustained-Action Opioids

Opioid Dosage Form	Percentage of Subjects	Mean Daily Dose (Range)
Oxycodone SR, oral	45%	141 (60–400) mg
Morphine sulfate SR, oral	16%	168 (60–330) mg
Methadone, oral	15%	97 (35–200) mg
Fentanyl, transdermal	24%	1500 (600–2400) μg

was used for DHEAS in 1 woman, TT in 1 woman, and E2 in 5 women.

Our study was approved by the Mercy Medical Center Institutional Review Board. Informed consent was obtained from all subjects. Statistical analyses were performed manually by the author by using the χ^2, Student *t* double-tailed, and Spearman's rho analysis techniques.

Results

Opioid dosage forms, with the percentage of subjects consuming each, plus mean and range of daily doses, are listed in Table 1. Fifty-five percent of opioid consumers also used supplemental short-acting opioids, usually hydrocodone or oxycodone, with consumption usually fluctuating from day to day.

Table 2 presents characteristics of opioid-consuming and control women who retained at least one ovary plus those who had undergone bilateral oophorectomy. Opioid consumers were younger and more often smokers in both groups and were more often obese among women with intact ovarian tissue.

Among women aged 30 to 50 years, nonsurgical amenorrhea had developed in 52% of opioid consumers and 20% of control subjects ($P < .05$). Fig 1 illustrates menopausal ages of women who had begun use of sustained-action opioids before age 50 and of opioid nonconsumers.

Table 2. Characteristics of Subjects

	Opioid Consumers	Control Subjects	P Value
Patients with intact ovarian tissue			
Number	31	42	
Age (avg) ± SD (y)	45.9 ± 10.6	53.9 ± 11.2	$P < .02$
BMI (avg) ± SD kg/m^2	30.4 ± 6.3	24.3 ± 5.0	$P < .002$
Smokers (%)	16 (52%)	0 (0%)	$P < .001$
Unilateral oophorectomy (%)	2 (6%)	3 (8%)	NS
Hysterectomy without bilateral oophorectomy	6 (19%)	3 (7%)	NS
Patients with bilateral oophorectomy			
Number	16	27	
Age (avg) ± SD (y)	52.9 ± 10.7	60.3 ± 9.6	$P < .05$
BMI (avg) ± SD (kg/m^2)	25.3 ± 5.6	27.5 ± 5.4	NS
Smokers (%)	11 (61%)	0 (0%)	$P < .001$
Age at oophorectomy (y)	38.6 ± 9.6	43.9 ± 7.12	NS

Abbreviations: BMI, body mass index; NS, not significant.

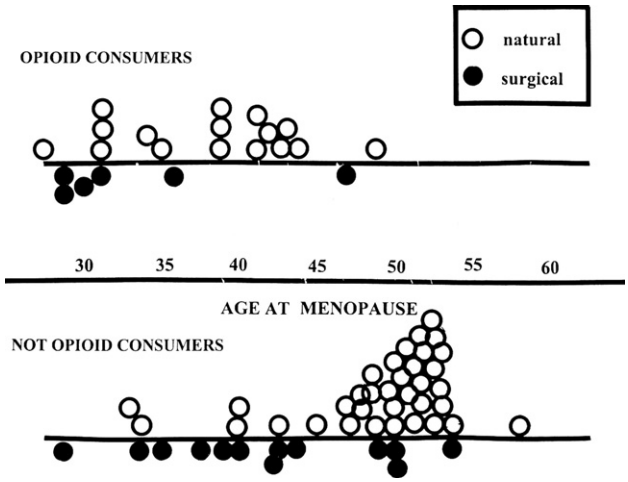

Figure 1. Age at menopause in women beginning sustained-action opioid use before 50 and in opioid nonconsumers.

Fig 2 illustrates the age at onset of menopause associated with the commencement of sustained-action opioid use among the 29 women who had been premenopausal at the onset of sustained-action opioid use before age 50. No women had become pregnant during use of sustained-action opioids, 8 had amenorrhea during the first year of sustained-action opioid use, 8 had amenorrhea at a later date, often during increased opioid use, 5 underwent hysterectomy, and 8 continued regular menses at the time of evaluation at an average age of 44 years (range, 37–49).

Table 3 presents average ages and values for hormones and SHBG in opioid-consuming women and control subjects with associated *P* values for this difference plus normal values for our laboratory. Among women aged 30 to 50 with intact ovarian tissue, opioid consumers demonstrated average hormone values that were 48% to 57% of those in control subjects. Among opioid-consuming

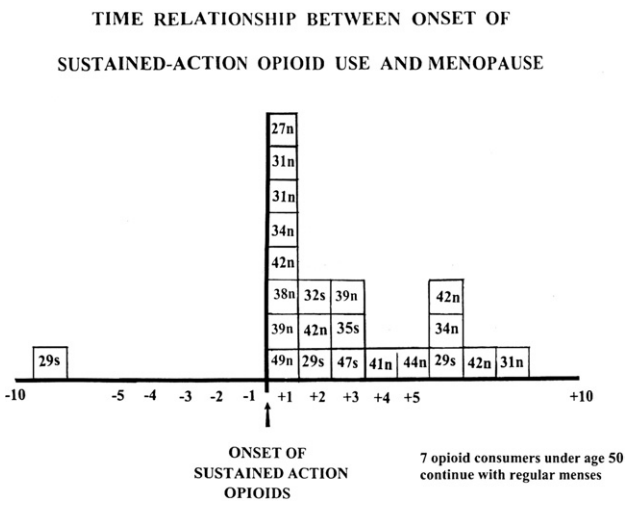

Figure 2. Onset of menopause before age 50 among opioid consumers related to onset of sustained-action opioid use. Boxed numbers indicate age at menopause (n, nonsurgical menopause; s, surgical menopause).

Table 3. Sex Hormone and SHBG Values of Opioid-Consuming Women and Control Subjects With Intact Ovarian Tissue and No Estrogen Therapy Analyzed by Age

	Opioid Consumers	Control Subjects	P Values	Normal Range
Ages 30–50				
Number	21	16		
Age (avg) ± SD (y)	39.3 ± 4.9	42.7 ± 3.5	NS	
Total testosterone ± SD (ng/dL)	30.7 ± 21.5	54.4 ± 10.3	< .001	14–76
SHBG ± SD (nmol/L)	63.2 ± 32.7	70.3 ± 27.1	NS	18–114
Free testosterone ± SD (pg/mL)	4.0 ± 3.5	7.0 ± 2.4	< .01	1–9
Estradiol ± SD (pg/mL)	63.2 ± 56.7	132.3 ± 108.1	< .05	30–230
DHEAS ± SD (μg/dL)	51.2 ± 52.1	113.3 ± 53.7	< .01	40–300
Ages 51–75				
Number	10	26		
Age (avg) ± SD (y)	59.6 ± 7.8	59.4 ± 6.5	NS	
Total testosterone ± SD (ng/dL)	24.6 ± 16.6	36.7 ± 17.7	NS	10–80
SHBG ± SD (nmol/L)	63.3 ± 41.7	62.2 ± 28.9	NS	18–114
Free testosterone ± SD (pg/mL)	3.9 ± 2.3	5.8 ± 3.9	< .04	1–9
Estradiol ± SD (pg/mL)	18.7 ± 9.3	29.7 ± 25.2	NS	11–61
DHEAS ± SD (μg/dL)	33.9 ± 24.6	66.5 ± 41.3	< .02	18–120

Abbreviations: SHBG, sex hormone–binding globulin; DHEAS, dehydroepiandrosterone sulfate; NS, not significant.

women over age 50, average hormone values were similarly 52% to 66% of those in control subjects. Average SHBG values were unrelated to opioid use. All smokers in our study were also opioid consumers. Among all opioid consumers, average SHBG values were 37% higher in smokers than in nonsmokers (72.3 ± 29.4 vs 52.6 ± 33.3 nmol/L) ($P < .05$), whereas average FT levels were lower (3.48 ± 2.84 vs 5.62 ± 3.21 pg/mL) ($P < .05$). BMI values, DHEAS values, and daily opioid dose were unrelated to smoking habits.

Table 4. Sex Hormone and SHBG Values of Opioid-Consuming Women and Control Subjects Without Ovaries Analyzed by Their Use of Oral Estrogen Replacement

	Opioid Consumers	Control Subjects	P Values
No oral estrogen therapy			
Number	9	16	
Total testosterone ± SD (ng/dL)	27.4 ± 20.4	43.9 ± 19.2	NS
SHBG ± SD (nmol/L)	57.7 ± 21.6	55.7 ± 25.6	NS
Free testosterone ± SD (pg/mL)	3.9 ± 2.4	6.4 ± 2.8	< .05
Estradiol ± SD (pg/mL)	27.4 ± 33.0	42.3 ± 21.0	NS
DHEAS ± SD (μg/dL)	40.6 ± 19.4	65.3 ± 44.7	NS
Oral estrogen therapy			
Number	7	11	
Total testosterone ± SD (ng/dL)	27.6 ± 14.7	34.4 ± 24.6	NS
SHBG ± SD (nmol/L)	172.2 ± 50.7	148.9 ± 93.2	NS
Free testosterone ± SD (pg/mL)	1.8 ± 1.1	2.9 ± 1.8	NS
DHEAS ± SD (μg/dL)	16.8 ± 9.3	87.5 ± 51.4	< .05

Abbreviations: SHBG, sex hormone–binding globulin; DHEAS, dehydroepiandrosterone sulfate; NS, not significant.

Table 4 presents sex hormone, DHEAS, and SHBG values for oophorectomized women grouped by their current use or nonuse of replacement estrogen therapy. Numbers of subjects were small in each subgroup. In oophorectomized women not consuming estrogen, hormone levels were 36% to 39% lower in opioid-consuming women than control subjects, but the difference only reaching statistical significance for FT. Among women with bilateral oophorectomy, those taking OER had higher SHBG values ($P < .001$) and lower FT values than similar women not using OER ($P < .05$ for opioid users and $P < .002$ for control subjects). Among women using OER, DHEAS levels were 80% lower in opioid consumers than in control subjects.

FT levels averaged higher and SHGB values averaged lower among women with a higher BMI, both among opioid consumers and control subjects, with FT values averaging at least 35% lower in opioid consumers than in control subjects with similar BMIs.

Figs 3 and 4 present FT and E2 levels, respectively, in opioid consumers and control subjects with retained ovarian tissue. The shaded areas indicate normal values for our reference laboratory.

Fig 5 presents LH and FSH values for women with retained ovarian tissue, grouped by opioid use and menopausal status. Two opioid consumers with hysterectomy before age 40 are not included. Average LH and FSH values were 70% to 73% lower among opioid-consuming postmenopausal women than control subjects ($P < .001$), with median values for LH of 4.1 and 32.5 mIU/mL, and, for FSH, 7.1 and 71.0 mIU/mL.

Among postmenopausal women, higher daily consumption of sustained-action opioids was associated with lower LH and FSH values, independent of age and BMI ($P <. 05$). FT levels were not clearly related to the type of sustained-action opioid consumed, the duration of it use, or to its daily dose, either in women with or

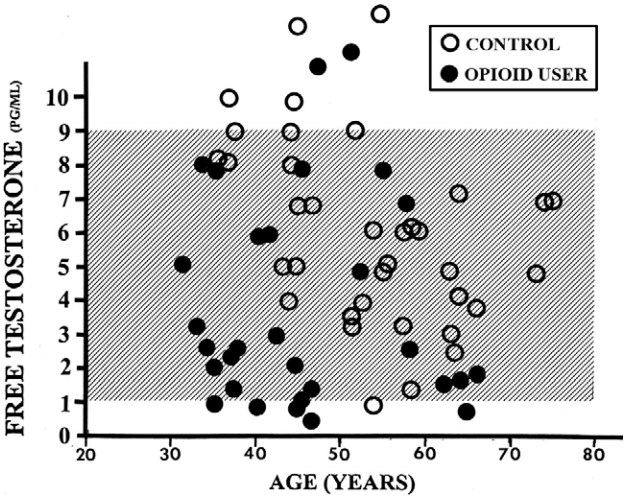

Figure 3. Free testosterone levels in opioid-consuming and control women.

without ovarian tissue. Forty-five of 49 (92%) opioid-consuming women complained of fatigue, depression, diminished libido, or diminished sexual satisfaction. Five of 49 opioid-consuming women had sustained osteoporotic fracture before age 60, compared with 1 of 68 control subjects ($P < .05$). DHEAS values in 55% of opioid consumers and control subjects had been reported earlier.[13] TT, FT, SHBG, DHEAS, and E2 values of these women were similar to those of the 45% not previously reported.

Discussion

This study demonstrates lower FT, TT, E2, LH, FSH, and DHEAS levels in women who chronically consume opioids in sustained-action oral or transdermal dosage forms than in non–opioid-consuming control subjects. Our observations support opioid-associated inhibition of both ovarian and adrenal testosterone formation, due to opioid-induced hypogondotrophic hypogonadism plus opioid-induced inhibition of adrenal androgen production. The absence of these changes in patients with chronic pain untreated by opioids[1,26] and their rapid induction after opioid administration to pain-free subjects[17,22] and presence in chronic opioid consumers without pain[40] support the concept that they are opioid-induced and unrelated to the presence of pain. The dose-related decrease in DHEAS levels previously demonstrated among both male and female opioid consumers[12] is now confirmed among women not included in our earlier report.

Our observations extend those of Abs et al[1] and others[18,34] who documented hypogondotrophic hypogonadism but did not report testosterone levels in women receiving long-term intrathecal opioid therapy. Many of their patients manifest amenorrhea or hypomenorrhea, diminished libido, sexual dysfunction, fatigue, and depression, symptoms also frequently present in our opioid-consuming subjects.

Opioid-associated hypogonadotrophic hypogonadism in both sexes is thought to largely result from opioid-induced inhibition of hypothalamic gonadotrophin releasing hormone (GnRH) production,[15] which cascades into diminished gonadal sex hormone production. Additional direct opioid inhibition of pituitary and gonadal tissues is suggested by opioid-induced decreases in LH production by cultured rat pituitary cells,[5] of testosterone production by rat Leydig cell cultures,[50] and of androgen production by porcine ovarian theca cells.[24]

Opioid inhibition of adrenal androgen production may have both central and peripheral components. Opioids inhibit hypothalamic corticotrophin-releasing hormone (CRH) production, cascading into inhibition of corticotrophin (ACTH) and cortisol[21,32,37] production. DHEAS production is also partially CRH and ACTH dependent,[34] but direct adrenal opioid-induced inhibition of DHEAS production is suggested by greatly depressed DHEAS levels during systemic opioid therapy,[13] in contrast to the normal levels during intrathecal therapy,[1] whereas ACTH levels remain normal in both groups.[1,11]

The presence of local factors prominent in the control of adrenal DHEAS production is highlighted by observations in castrated dogs with dexamethasone-induced adrenal suppression, where ACTH concentrations required for the induction of DHEAS formation were 10,000 times those necessary to stimulate cortisol formation,[35] and by stimulation by CRH of DHEAS production from human adrenal tissue over that of cortisol.[23,46] A role for CRH in the local adrenal control of DHEAS production is also supported by opioid inhibition of CRH production, coupled with the presence of CRH receptors[39] and high concentrations of CRH[41] in normal adult human adrenal tissue.

In premenopausal women, testosterone is produced in approximately equal amounts from adrenal and ovarian tissues,[4,29] 25% directly from the adrenal glands, 25% directly from the ovaries, and 50% from androstenedione conversion within peripheral tissues. Androstenedione is 25% derived from adrenally generated DHEA and DHEAS, with the balance equally produced directly from ovarian and adrenal tissues. In postmenopausal women, testosterone production from adrenal sources is characteristically maintained for many years, whereas that

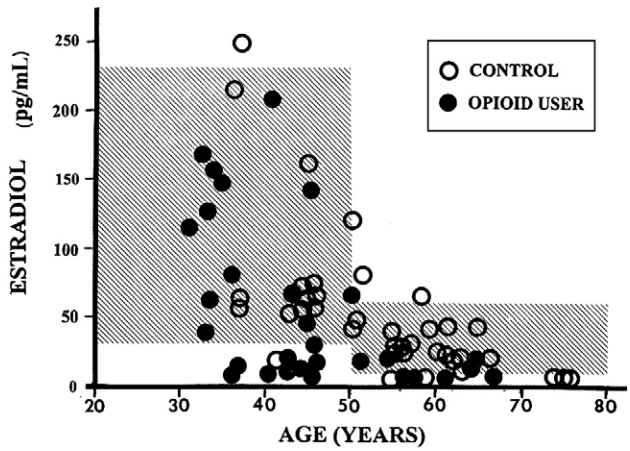

Figure 4. Estradiol levels in opioid-consuming and control women.

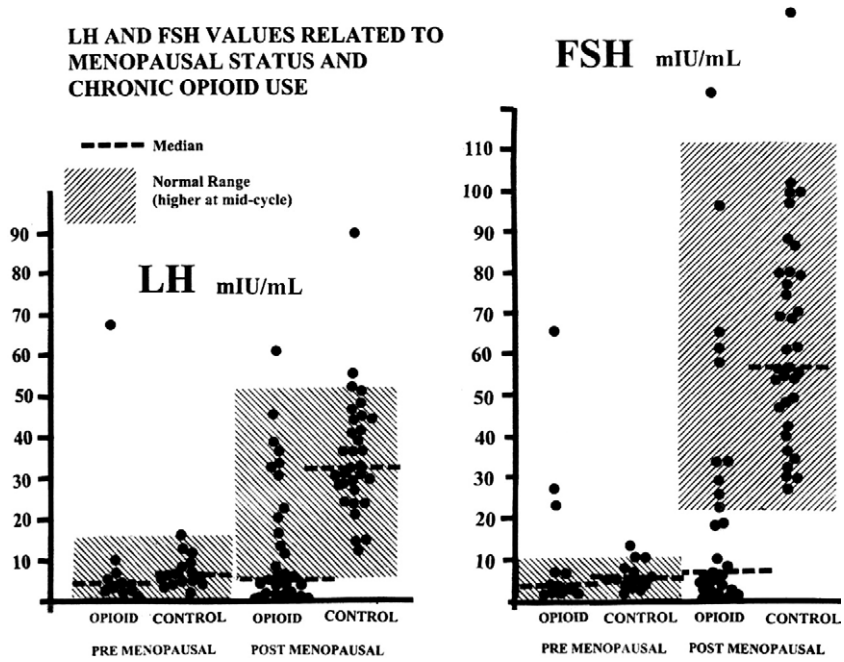

Figure 5. LH and FSH values in premenopausal and postmenopausal opioid consumers and control subjects.

from ovarian sources is maintained less predictably but persists for many years in at least 50% of women.[6,29]

Near-total opioid inhibition of ovarian androgen production is supported by the similar TT and FT levels in opioid consumers with and without ovaries. Contributing to this ovarian inhibition are profound opioid-induced suppression of LH formation, denying its stimulation of testosterone production, perhaps coupled with direct opioid-induced suppression of ovarian testosterone formation.[24]

Opioid-induced inhibition of adrenal androgen production is supported among our oophorectomized women by the 40% lower DHEAS, TT, and FT levels among opioid-consumers than control subjects and by similarly low levels of DHEAS among men consuming sustained-action oral or transdermal opioids.[13]

Estradiol in premenopausal women is largely of ovarian origin, produced by aromatase-enhanced transformation of testosterone, a process stimulated by FSH. The lower estradiol levels in our opioid consumers appear likely to reflect opioid-induced lowering of both adrenal and ovarian testosterone production, coupled with opioid-induced lowering of FSH levels. Opioid-associated menstrual changes in women using systemic[42] or intrathecal[1] opioids appear to reflect the 30% to 70% lower estrogen and gonadotrophin levels in both groups.

The hypogonadotrophic amenorrhea of opioid-consuming patients differs from the hypergonadotrophic amenorrhea characteristic of spontaneous menopause among nonopioid consumers. Opioid-associated amenorrhea occurs in women whose residual primordial germ cells lack stimulation for development and fertility, whereas spontaneous menopause is characterized by profound depletion of primordial germ cell numbers with associated infertility. Most irregular menses in women receiving intrathecal opioids represent anovulatory cycles,[1] but potential fertility in amenorrheic opioid consumers is supported by pregnancies among heroin addicts during methadone maintenance[16] and occasional ovulation during intrathecal opioid therapy.[1]

OER decreases FT levels by 3 mechanisms, by inhibiting LH formation, thereby diminishing ovarian testosterone production, by augmenting SHBG formation, which lowers the unbound fraction of circulating testosterone,[20,43-45] and by depressing adrenal androgen synthesis.[7,45] FT levels were lower in our oophorectomized women consuming OER than in similar women without OER, both among opioid consumers and control subjects, confirming inhibition of adrenal androgen production by OER. The lowest FT levels in our cohort occurred in opioid consumers using OER, suggesting that factors lowering the FT levels during opioid consumption and OER are additive and may be independent of each other.

Altered pain sensitivity may occur in women with opioid-associated endocrinopathy. Tennant[49] reported improved pain control during testosterone supplementation in 10 of 14 testosterone-deficient, opioid-consuming women, 7 of whom concurrently diminished opioid consumption without sacrificing pain control. Forman et al[19] demonstrated greatly increased pain sensitivity after castration of female mice, with subsequent estradiol therapy either decreasing or augmenting this increased pain sensitivity in response to different types of nociceptive pain.

The much higher frequency of cigarette smoking among our opioid consumers, the similar pattern in men,[11-13] similar observations by others,[31] and high

smoking frequency among methadone-maintained heroin addicts without chronic pain[40] may indicate the presence of characteristics in opioid consumers that increase their addiction potential or that OE may diminish the ability of patients to discontinue tobacco use.

Our study includes several weaknesses that we were unable to circumvent. Our opioid-consuming women were younger, exhibited higher BMIs, and were more frequently smokers than our control subjects. These differences, however, seem unlikely to contribute to the opioid-associated changes we report.

Testosterone levels in women decline progressively from adolescence to the menopause and remain reasonably stable thereafter, whereas DHEAS levels decline rapidly from the third through the seventh decades.[14] These patterns suggest that the younger average age of our opioid consumers would not have contributed to their lower testosterone and DHEAS levels.

Obese women characteristically have higher FT and lower SHBG levels than nonobese women,[3] a pattern confirmed in both our opioid consumers and control subjects that suggests that the higher average BMI of our opioid consumers would not have contributed to their lower FT levels.

Smoking has been unrelated to TT or FT values in several large population-based studies[6,25,27] and associated with higher TT values in others.[10,47] SHBG values have been reported to be similar to[25] or 10% to 15% higher[10,28,33] in smokers. SHBG values were higher in the smokers among 16 opioid- consuming men[13] and 70% higher than in control subjects among male heroin addicts[52], many of whom smoked their heroin, and some of whom were methadone-maintained, a population in which most men also smoke tobacco.[40] Among our opioid consumers, SHBG values in smokers averaged 37% higher than those of nonsmokers, indicating a contribution by their SHBG to the low FT levels of our smoking opioid-consuming women.

DHEAS levels have averaged 35% higher among smoking women in several large studies[25,28] but differed little between our smoking and nonsmoking opioid consumers, suggesting that smoking did not contribute to lowering of DHEAS values among our opioid consumers.

FT and TT levels were depressed to a similar degree among opioid-consuming women over age 50 whether or not ovarian tissue was present, suggesting near-complete inhibition of ovarian testosterone production and partial inhibition of adrenal androgen production. FT and TT values, however, were also similar among our control subjects with and without ovaries, in contrast to the 16% to 40% lower testosterone levels presents among oophorectomized women in large surveys.[6,14,27,47] Each of these populations, however, demonstrated wide variations in FT and TT values, suggesting that the similar FT and TT levels in our oophorectomized and intact control subjects and a similar pattern in 2 other similarly small cohorts[9,48] probably reflect small sample sizes.

The clinical significance of the opioid-associated hormone deficiencies that we have demonstrated is not established. Related studies suggest contributions by these changes to opioid-associated hyperalgesia, depression, fatigue, vasomotor phenomenon, impaired fertility, and osteoporosis. Clinical improvement during short-term replacement therapy with DHEA or testosterone in women with deficiencies of these hormones of similar degree to those in our opioid consumers but due to adrenal or pituitary disease suggest a potential for modifying these opioid-associated signs and symptoms by replacement of these deficient hormones, including a need for careful related controlled investigations.

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