Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Maurizio Guida, Alessia Rega, Imma Vivone, Gabriele Saccone, Laura Sarno, Costantino Di Carlo, Carmen Imma Aquino & Jacopo Troisi (2019): Variations in sleep associated with different types of hormonal contraceptives, Gynecological Endocrinology, DOI: 10.1080/09513590.2019.1640204

To link to this article: https://doi.org/10.1080/09513590.2019.1640204

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1640204

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ORIGINAL ARTICLE

Variations in sleep associated with different types of hormonal contraceptives

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ABSTRACT

Progesterone and some of its metabolites are neuroactive steroids that affect sleep by increasing melatonin secretion and stimulating GABA-A receptors. The effect of progestogens in hormonal contraceptives on sleep has not been thoroughly investigated. This observational study assessed possible associations in sleep changes induced by estrogen–progestogens in contraceptives in 108 women between the ages of 20 and 50 years. We assessed mean nightly sleep time with a 31-day sleep diary, and subjective sleep quality with the five subjective subscores of the Pittsburgh Sleep Quality Index (PSQI). Included women were of childbearing age, healthy, sexually active and had been using a hormonal contraceptive method (pill, intrauterine system (IUS), subcutaneous implant, vaginal ring) for at least six months. Results were compared to a matched control group that did not use hormonal contraceptives. The longest mean nightly sleep time, compared to control (450 min), occurred in women who used progestogen-only oral contraception (510 min), followed by IUS delivery of levonorgestrel 13.5 mg (480 min) and oral ethinylestradiol 0.02/0.03 mg plus gestodene 0.075 mg (475 min). Global subjective sleep quality was influenced most by the administration of etonorgestrel 0.120 mg/ethinylestradiol 0.015 mg via the vaginal route. Our results show that low-doses of progestins affect various aspects of sleep, and that this is influenced by the route of administration.

ARTICLE HISTORY
Received 21 January 2019
Revised 17 June 2019
Accepted 2 July 2019
Published online 17 July 2019

KEYWORDS
Hormonal contraceptives; sleep quality; progestin; sleep duration; administration route

Introduction

The active metabolites of progesterone have a sedative effect on the central nervous system (CNS) that has been exploited for the treatment of sleep disorders through intranasal administration [1]. Indications that progesterone has hypnogenic effects include the increased drowsiness during pregnancy, when progesterone levels are very high [2,3], and sleep alterations in (peri)menopause with reduction of sleep time when estrogen and progesterone levels are low [4–9]. Administrations of high-dose progesterone (300 mg) can re-establish normal sleep time in post-menopausal women with sleep disorders [10]. The effect is based on a benzodiazepine-like effect due to the allosteric enhancement of GABA-A receptor signaling by progesterone metabolites such as allopregnanolone [11,12].

EEG sleep architecture is influenced by changes in sex hormone levels during the menstrual cycle and by hormonal contraceptives [13–16]. Baker et al. found that women taking oral contraceptives had more stage-2 non-rapid eye movement sleep and less slow wave sleep than naturally cycling women [14]. A small retrospective study conducted by Burdick et al., confirmed that women taking oral contraceptives had less slow wave sleep, and also reported that they had shorter sleep latency and REM latency than controls [15]. These observations have prompted the suggestion that hormonal contraceptives be considered for treating sleep disorders in premenopausal women [17].

To date, nothing has been reported regarding the influence of hormonal contraceptives on sleep duration and subjective sleep quality. Our pilot study evaluated whether progestins used in contraception are associated with sleep changes in duration and quality.

Materials and methods

Study design

This was a cross-sectional pilot study to evaluate associations between the use of hormonal contraceptives and sleep, with particular attention to the role of progesterone. We also assessed whether contraceptive administration route is associated with differences in sleep.

Included women were of childbearing age, healthy, sexually active and had been using a hormonal contraceptive method (pill, intrauterine system (IUS), subcutaneous implant, vaginal ring) for at least six months.

BMI was also included in the selection criteria, because the overweight can interfere with quality/quantity of sleep. BMIs were, however, calculated and the t test excluded a significant difference between the treated groups and the control group ($p < .05$).

Exclusion criteria were as follows: women seeking pregnancy; abuse of alcohol or psychoactive substances; neurological,

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Supplemental data for this article can be accessed here.

Table 1. Group compositions according to hormonal contraceptive.

Group	*N*	Mean age	Progestin	Estrogen
Control	19	33.2	–	–
Oral				
Progestin only	5	31	Desogestrel 0.075 mg/Dienogest 2 mg	–
Clormadinone	5	33.3	Clormadinone 2 mg	EE 0.03 mg
Drospirenone	14	37.2	Drospirenone 3 mg	EE 0.02 – 0.03 mg
Gestodene	8	35	Gestodene 0.075 mg	EE 0.02 – 0.03 mg
Dienogest	7	32.1	Dienogest 2 mg	EE 0.03 mg
Levonorgestrel	4	33	Levonorgestrel 0.1 mg	EE 0.02 mg
Natural estrogens	10	33.6	Nomegestrol 2.5 mg/Dienogest 2 mg	E 1.5 mg/EV 2 mg
IUS				
IUS 1	10	34.9	Levonorgestrel 13.5 mg	–
IUS 2	10	44.6	Levonorgestrel 20 μ/24 h	–
Subcutaneous	10	37.3	Etonorgestrel 68 mg	–
Vaginal Ring	6	30.7	Etonorgestrel 0.120 mg	EE 0.015 mg

E: estradiol; EE: ethinylestradiol; EV: estradiol valerate; IUS: intrauterine (hormone delivery) system.

psychiatric, renal, hepatic, cardiovascular, endocrine or gynecological disorders; overweight (BMI $\geq$ 30); female sexual dysfunction, use of drugs (other than contraceptives).

Study population

Based on these criteria, 125 women between the ages of 20 and 50 years were enrolled between May 2017 and January 2018 at the Fertility Control Clinic at the "San Giovanni Di Dio and Ruggi D'Aragona" University Hospital in Salerno, Italy. Most women were using oral contraceptives (53), followed by IUS (20), subcutaneous implant (10) and vaginal ring (6); whereas, women who met all criteria except the use of a hormonal contraceptive were recruited as a control group (19). Differences in hormone composition, dosage, and administration route necessitated subdividing women (Table 1).

Data collection

The sleep diary was printed according to a table format in which sleep time and wake-up time were requested. The average minutes of sleep per night and then the average ones in 30 days were calculated, they were compared by *t*-test ($p < .05$).

Sleep time was recorded with a sleep diary compiled autonomously each morning for 31 days starting from recruitment [18]. Sleep quality was assessed at the end of the 31-day period with the Pittsburgh Sleep Quality Index (PSQI) [19]. We considered only the 5 PSQI subscores addressing subjective sleep quality and relied on the sleep diary for a complete assessment. Global PSQI score was not significative. Instead, we assigned numerical values from 0 (no sleep problems) to 3 (highest impairment) to each of the 5 subjective subscores, and used the mean as a global subjective sleep score.

Statistical analysis

Data from analysis of the questionnaires are expressed as mean ± SEM. Statistical differences were evaluated by means of ANOVA (one way) and/or Student's *t*-test and/or chi-squared test and/or Spearman test. Values of $p < .05$ were considered significant.

Results

Sleep duration

Minutes of sleep per night was assessed according to the type of hormonal contraceptive and administration route to determine if an association existed between sleep and contraceptive use (Figure 1). Compared to the control group, women who used progesterone-based oral contraceptives (progestin only group) recorded the most sleep, followed by the oral gestodene group and IUS-1 group. Groups in which the estrogen/progestin ratio was similar to physiological did not differ significantly from control.

Analysis of age and sleep duration

We assessed the relationship between age and sleep time, finding that in the control group increasing age is associated with longer sleep duration ($p < .05$; Spearman test) (Supplemental Figure 1). There was no significant correlation between age and sleep duration in any of the groups using hormone contraceptives; external factors including the administration of progestins appear to be more important than age in this population.

Subjective sleep quality

Sleep quality was assessed with the 5 subjective subscales of the PSQI. The data were standardized as group percentages and compared to control using a chi-squared test. Women in the vaginal, IUS 1, oral progestin only, oral gestodyne, and oral natural estrogens groups reported significantly less sleep disturbance, compared to the control group. Sleep disturbance was significantly worse than control in the IUS2, oral clormadinone and oral dienogest groups (Supplemental Figure 1).

Sleep latency was reported less frequently than control in the subcutaneous, vaginal, IUS 2, oral progestins only, oral clormadinone, oral gestodiene, oral dienogest, and oral natural estrogens groups; whereas, more women in the oral levonorgestrel group reported sleep latency (Supplemental Figure 1).

PSQI results are provided in Supplemental Figures 2–5, and summarized here below. The rate of daytime somnolence was higher in the vaginal, oral gestodene, oral clormadinone and oral natural estrogens groups. This phenomenon was less common in the IUS 2, oral dienogest and oral levonorgestrel groups. There was no significant difference between groups regarding the use of sleep-inducing drugs. Overall sleep quality was better than the

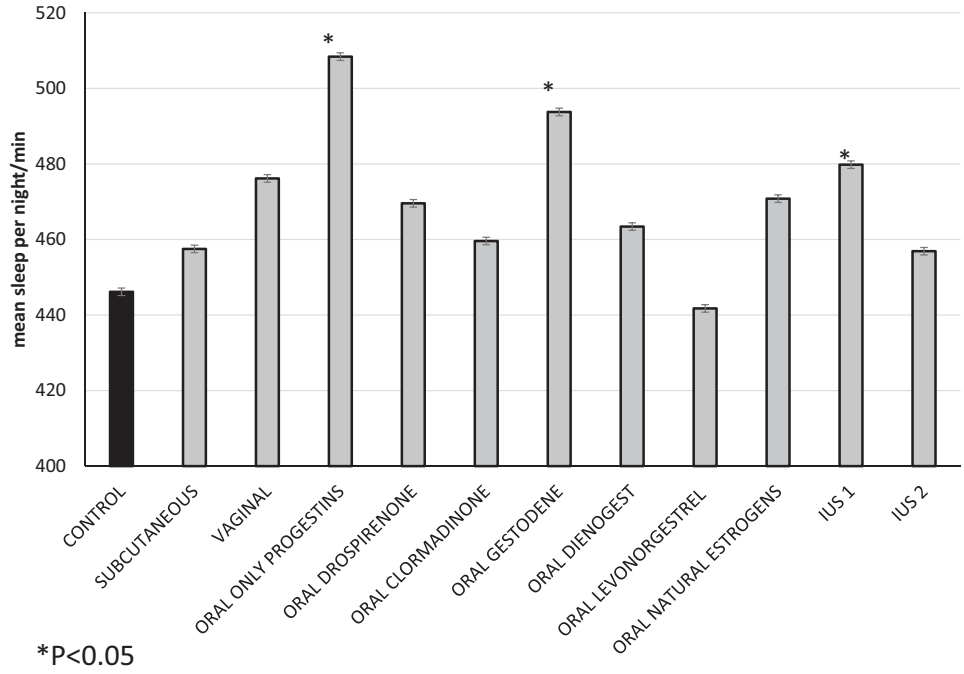

Figure 1. Mean nightly sleep duration according to contraceptive group from 31-day sleep diary.

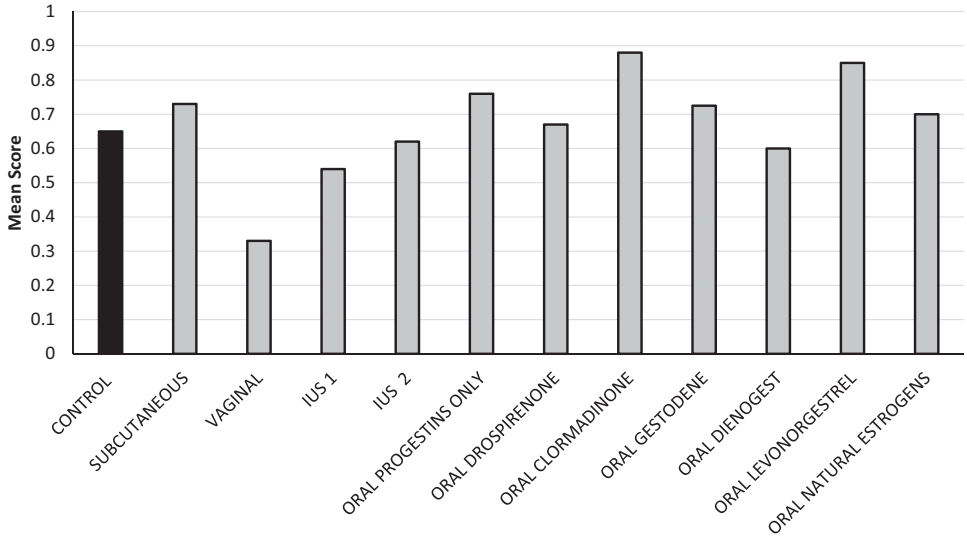

Figure 2. Global subjective sleep quality, expressed as the mean of the subjective sleep sub-scores.

control in all groups except oral dienogest and oral levonorgestrel.

Global subjective sleep quality based on PSQI subscores was higher in the vaginal group, followed by IUS-1, oral dienogest and IUS-2 (Figure 2).

Regarding depot-type administration routes, subcutaneous administration was associated with less sleep latency and better overall sleep quality compared to control ($p < .01$ for both). Vaginal delivery was associated with less sleep latency and disturbance with respect to control ($p < .0001$ for both); daytime drowsiness was reported less and overall sleep quality was better than control ($p < .05$ for both). IUS administration of levonorgestrel 13.5 mg was associated with increased sleep time compared to the control (480 min vs. 450 min), less sleep disturbance ($p < .05$) and better overall sleep quality ($p < .0001$). The group using IUS delivery of levonorgestrel 20 µg/24 h had more sleep disturbance than control ($p < .05$), and less daytime somnolence ($p < .0001$). Overall sleep quality was better than that of the control group ($p < .0001$).

Oral hormonal contraceptives were assessed separately according to their composition. Women using compositions that contained only progestins had longer mean nightly sleep times than the control (510 min vs. 450 min), less sleep latency and disturbance ($p < .0001$ for both), but daytime dysfunction was more prominent ($p < .0001$). In spite of this, overall sleep quality was better than control ($p < .0001$). Oral clormadinone (EE 0.03 mg/clormadinone 2 mg) was associated with less sleep latency but more sleep disturbance and daytime dysfunction, but overall sleep quality was better than control ($p < .0001$ for all). Oral gestodene (EE 0.02–0.03/gestodene 0.075 mg) was associated with longer sleep time compared to control (475 vs. 450), and less sleep latency and disturbance ($p < .0001$ for both); it increased daytime dysfunction, but overall sleep quality was better than control ($p < .001$ for both). Oral dienogest (EE 0.03 mg/dienogest

2 mg) was associated with less sleep latency ($p < .0001$), while sleep disturbance and daytime dysfunction were more common ($p < .05$ for both). Oral levonorgestrel (EE 0.02 mg/levonorgestrel 0.1 mg) was associated with more sleep latency ($p < .05$), while improving daytime dysfunction and overall sleep quality ($p < .0001$ for both). Women who used oral preparations containing natural estrogens (1.5 mg–2 mg), combined with nomegestrol 2.5 mg and dienogest 2 mg, reported less sleep latency ($p < .0001$) and disturbance ($p < .001$), more daytime dysfunction ($p < .0001$) but overall sleep quality was better than control ($p < .05$).

Discussion

We have studied the associations of various hormonal contraceptives on female neuro-psycho-physiology [20–25].

Progesterone and some of its metabolites have a strong effect on sleep, compared to other sex hormones. Any improvement in terms of quantity and quality of sleep could have a positive impact on lifestyle [10,26].

Progestins, moreover, seems to potentiate the generation of sleep spindles, which may have significant implications for research that examines the role of these waveforms in learning, development, and mental illness [27].

To study the effects of progestin contraceptives, we grouped women according to hormonal composition, dose and route of administration, because this can influence the systemic hormone levels and their stability. We then assessed nightly sleep time and subjective aspects of sleep quality compared to the control group not using hormonal contraceptives.

Age is one of the parameters that affects sleep in women [28,29]. Our data show a correlation between age and sleep duration but suggest that the effect of age on sleep may be overcome by administering progestogen-based drugs.

The etonorgestrel 0.120 mg/ethinyl estradiol 0.015 mg formulation with vaginal administration had the greatest overall effect on sleep characteristics. This difference may be due to the composition of this formulation, or to the vaginal administration route, which provides constant serum hormone levels. The route of administration has a dominant effect on blood hormone concentrations. Oral administration is subject to hepatic first pass metabolism which does not affect depot administration (vaginal ring, subcutaneous, IUS). Potential benefits of depot delivery include lower dosing and lower systemic exposure, which may reduce the incidence of adverse effects while achieving the same pharmacodynamic effect. The transdermal patch, pill, and vaginal ring provide women with more control over their contraception, although the depot methods have the advantage of extended maintenance of constant serum levels [30].

Our study has several limitations. Our analyses are based on self-reported sleep times and sleep quality. We did not measure objective sleep parameters and how hormonal contraceptives influenced sleep architecture. Whereas such changes have been reported previously [1,14,15], the sleep EEG modifications have not been compared with the qualitative sleep data. The PSQI is a validated tool with appropriate correlations to objective sleep measures. We used the nightly sleep diary to avoid recall bias and memory issues when recording sleep data over the 31-day study.

This is a pilot study and the number of samples per group is small, but *t*-test showed statistical significance matching between the control group and the treated groups ($p < .05$). We intend to expand the sample to improve the results obtained so far.

It was not possible to group the groups because the aim of the study was to determine the sleep characteristics of women taking different concentrations of estrogens and/or progestins (and therefore different types of pharmaceutical preparations).

Finally, while 108 women completed the study the heterogeneous mix of hormone combinations and delivery routes necessitated dividing the women into relatively small groups in order to interpret effects of different progestins and routes, with a negative impact on statistical power.

However, to our knowledge, this is one of the first few studies to address associations between hormonal contraceptives and sleep data, while considering also hormone composition, dosage and administration route. These preliminary results must be confirmed with larger studies.

Conclusions

Longer sleep duration does not necessarily correlate with higher sleep quality.

Clinical studies are needed to replicate these results in larger samples and to determine whether hormonal contraceptives could improve sleep quality in women with sleep problems.

Disclosure statement

No potential conflict of interest was reported by the authors.

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