Associations of Menstrual Cycle and Progesterone-to-Estradiol Ratio With Alcohol Consumption in Alcohol Use Disorder: A Sex-Separated Multicenter Longitudinal Study

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Objective: Alcohol use disorder (AUD) constitutes a critical public health issue and has sex-specific characteristics. Initial evidence suggests that progesterone and estradiol might reduce or increase alcohol intake, respectively. However, there is a need for a better understanding of how the menstrual cycle in females and the ratio of progesterone to estradiol in females and males influence alcohol use patterns in individuals with AUD.

Methods: In this sex-separated multicenter longitudinal study, the authors analyzed 12-month data on real-life alcohol use (from 21,460 smartphone entries), menstrual cycle, and serum progesterone-to-estradiol ratios (from 667 blood samples at four individual study visits) in 74 naturally cycling females and 278 males with AUD between 2020 and 2022, using generalized and general linear mixed modeling.

Results: Menstrual cycle phases were significantly associated with binge drinking and progesterone-to-estradiol ratio. During the late luteal phase, females showed a lower predicted binge drinking probability of 13% and a higher predicted marginal mean of progesterone-to-estradiol ratio of 95 compared with during the menstrual, follicular, and ovulatory phases (binge drinking probability and odds ratios vs. late luteal phase, respectively: 17%, odds ratio=1.340, 95% CI=1.031, 1.742; 19%, odds ratio=1.523, 95% CI=1.190, 1.949; and 20%, odds ratio=1.683, 95% CI=1.285, 2.206; difference in progesterone-to-estradiol ratios, respectively: −61, 95% CI=−105.492, −16.095; −78, 95% CI=−119.322, −37.039; and −71, 95% CI=−114.568, −27.534). In males, a higher progesterone-to-estradiol ratio was related to lower probabilities of binge drinking and of any alcohol use, with a 10-unit increase in the hormone ratio resulting in odds ratios of 0.918 (95% CI=0.843, 0.999) and 0.914 (95% CI=0.845, 0.988), respectively.

Conclusions: These ecologically valid findings suggest that high progesterone-to-estradiol ratios can have a protective effect against problematic alcohol use in females and males with AUD, highlighting the progesterone-to-estradiol ratio as a promising treatment target. Moreover, the results indicate that females with AUD may benefit from menstrual cycle phase-tailored treatments.

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Alcohol use disorder (AUD) and excessive alcohol use are serious public health threats and impose a high burden on individuals, their families, and society as a whole (1). The prevalence rates of AUD are estimated to be between 4% and 5% among females, and between 12% and 15% among males in the Americas and Europe (1). (As we refer to sex rather than gender, we chose to use the terms female and male instead of the gender-related terms woman and man.)

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Although AUD is more prevalent in males, females progress more rapidly to AUD from the onset of alcohol drinking (2). To develop more effective treatment strategies, a better understanding of the mechanisms underlying AUD is crucial.

The sex differences in problematic alcohol use (1–3) and the effects of sex hormones on the brain reward system observed in animal experiments (4, 5) indicate that progesterone and estradiol may play a key role in AUD in females and males. A systematic review (6) found support for an association between higher estradiol levels and increased alcohol use in females, but inconsistent results in males. The review found, too, that the evidence was very limited on how progesterone is related to alcohol use in humans. In recent studies, high serum progesterone levels were correlated with lower craving for alcohol in postmenopausal females with AUD (7), and a decrease in progesterone in interaction with negative mood was associated with a higher likelihood of drinking alcohol (8).

For cocaine use disorder, results from animal studies suggest that in both sexes the administration of progesterone may serve as a potential treatment, whereas estradiol may be a risk factor (9). Interestingly, in female and male rodents, progesterone attenuates the reinforcing effects of cocaine, with reduced acquisition, escalation, and reinstatement of self-administration (10). In cocaine-dependent human females, high progesterone levels are associated with low stress- and cue-induced craving and anxiety (11), and the administration of progesterone to cocaine-dependent females and males leads to an increase of its metabolite, allopregnanolone, in plasma, with a reduction in craving, normalization of stress reactivity, and improvement of mood and cognitive performance (12, 13). Interestingly, estradiol sensitizes dopamine neurons in the ventral tegmental area (14) and increases cocaine-induced dopamine levels in the dorsal striatum of female rats (15), two key areas involved in the neurocircuitry of addictive behavior. Indeed, given its therapeutic potential, progesterone is of particular interest. However, it remains unclear whether the mentioned protective effects of progesterone related to cocaine use are also valid in individuals with AUD.

The menstrual cycle has commonly been utilized as a naturalistic setting to investigate behaviors related to the varying brain exposures to progesterone and estradiol in female samples. This involves low progesterone and estradiol levels during the follicular phase, low progesterone and peaking estradiol levels during the periovulatory phase, peaking progesterone and mildly elevated estradiol levels during the luteal phase, and falling progesterone and estradiol levels before the menstrual phase (16). In a tightly controlled within-person study of 22 naturally cycling young female university students, Martel et al. (17) found a lower likelihood of alcohol drinking in phases of high progesterone relative to estradiol saliva levels during the luteal phase. These effects were amplified for binge drinking (vs. any alcohol use) and were present on weekend days but not weekdays. Consistent with the findings reported above, these observations suggest that progesterone and estradiol may cause a decrease and an increase, respectively, in problematic alcohol use. However, two systematic reviews addressing changes in alcohol use across the menstrual cycle concluded that the data are inconsistent and subject to several limitations (18, 19). Most of the research used small convenience samples of college students, in a narrow age range. Moreover, a comparison of the studies is limited by inconsistent operationalization of menstrual cycle phase, unstandardized cycle phase designations (e.g., length, position), and varying definitions and assessment methods for alcohol use (e.g., retrospective self-reports, which are subject to recall bias [20]).

Overall, the literature on the effects of progesterone and estradiol on alcohol use patterns is limited. In particular, there is a lack of research investigating the associations between alcohol use patterns in females and males with AUD and the levels of progesterone relative to estradiol—the progesterone-to-estradiol ratio. This appears to be critical, because the progesterone-to-estradiol ratio represents an established marker of hormonal variation across the menstrual cycle and has been suggested to be a better predictor of behavior and physiology than progesterone and estradiol levels alone (e.g., 21–24). Similarly, we lack conclusive evidence on how alcohol use varies across the menstrual cycle in females with AUD and on whether the progesterone-to-estradiol ratio is also related to alcohol use patterns in males with AUD. The latter is very likely since progesterone and estradiol are relevant to the male organism (5, 25).

Females are still highly underrepresented in AUD research. Thus, separate investigations for females and males are necessary to avoid sex bias (26). In this study, we investigated activities of the progesterone-to-estradiol ratio in relation to alcohol use in both sexes. In premenopausal naturally cycling females with AUD, we used the menstrual cycle as a proxy for longitudinal changes in progesterone-to-estradiol ratios. We expected a lower probability of binge drinking and higher mean progesterone-to-estradiol ratios during the luteal phase than during the ovulatory phase. In males with AUD, we hypothesized that higher progesterone-to-estradiol ratios are associated with lower probabilities of binge drinking and of any alcohol use.

Of note, previous research indicates that the effects of progesterone and estradiol activity on alcohol use patterns differ between weekend days and weekdays (17), with weekend status as a permissive factor in the association between hormones and alcohol drinking and between varying severities of AUD, with stronger effects in mild AUD (27). Therefore, we investigated a sample of females and males with prevalently mild to moderate AUD and explored whether the interactions of menstrual cycle phases and the progesterone-to-estradiol ratio with weekend days versus weekdays and AUD severity affect alcohol use patterns. For further details on the hypotheses and research questions, see Figure S1 in the online supplement.

METHODS

Study Design and Sample Description

This 12-month follow-up cohort study was conducted within the framework of the Collaborative Research Center Transregio 265 (TRR 265) (28). Between February 2020 and July 2022, we screened 3,492 individuals. Of these, 672 females and males (self-reported sex) with mainly mild to moderate AUD were enrolled at three study sites in Germany (Charité–Universitätsmedizin Berlin, Technische Universität Dresden, and Central Institute of Mental Health Mannheim; TRR 265 cohort; preregistration: DRKS00020580; for general inclusion and exclusion criteria, see the online supplement). Written informed consent was obtained after the procedures had been fully explained. The project was carried out in Germany; predominantly White participants were included, but we did not ascertain ethnicity. The study design included four visits (at baseline and at follow-ups scheduled 4, 8, and 12 months after enrollment) and ecological momentary assessments (EMAs) every other day (29). The project was approved by the local ethics committees of Charité–Universitätsmedizin Berlin, Technische Universität Dresden, and Heidelberg University.

Seventy-four females were classified as premenopausal naturally cycling females. They reported having a regular cycle during the previous 3 months, of at least 21 days and no more than 35 days; reported not having used hormonal contraceptives or other hormones; reported the date of the last menses; and were not older than 42 years. This maximum age was based on age 50 as the median age at cessation of menses in females in Germany (30), with 8 years subtracted to account for perimenopause (31). We excluded females who reported use of hormonal intrauterine or vaginal devices, subdermal implants, contraceptive patches, or other hormonal methods. The study also included 278 male participants.

Data Sampling: Ecological Momentary Assessment

Participants were asked to submit information through a smartphone e-diary application every second day (for further details, see reference 29) across 365 days. They were reminded by an alarm at noon, which could be postponed until 8 p.m. For this project, we analyzed the e-diary entries on alcohol use, for which participants were asked the following questions: "Think about yesterday. Which and how many alcohol-containing drinks did you consume? Think about the day before yesterday. Which and how many alcohol-containing drinks did you consume?" (For the questions in German, see the online supplement.) The participants selected alcohol-containing drinks from a list with information on volume and alcohol content.

As illustrated in Figure S2 in the online supplement, we analyzed 4,863 entries from 74 naturally cycling females with AUD from 115 observation periods. These were coupled with two complete menstrual cycles oriented to the onset of the last menses which were reported during the four study visits. Similarly, in the male sample, we used 16,597 entries distributed around the four study visits and considered the progesterone-to-estradiol ratios from blood drawn during the study visits representative for these time windows. Response rates to queries on alcohol consumption were 69% (4,863 of 7,045) in the female sample and 66% (16,597 of 25,124) in the male sample; given the 365-day long-term assessment in real life, this indicates sound adherence rates. For sensitivity and robustness analyses, we analyzed EMA data on mood, social isolation, and responsiveness to rewards other than alcohol (i.e., alternative reward) (for details on the methods, see the online supplement).

Classification of Menstrual Cycle Phases

At every study visit, females were asked to answer the following questions: "During the previous three months, did you have a regular cycle? [Yes/No]. How long does your cycle last? [Less than 21 days/21 to 23 days/24 to 26 days/27 to 29 days/30 to 32 days/33 to 35 days/more than 35 days]. When did your last menstruation start? [Day|Month|Year]. Do you take contraceptives or other hormones? [Yes/No]." To classify the menstrual cycle phase, we used a recently recommended counting approach (32), shown in Table 1. The method takes into account individual differences in cycle length, which are mostly due to variances in the length of the follicular phase (31).

Quantification of Hormone Serum Concentrations

Blood samples were collected at each study visit. The vials were incubated at room temperature for 0.5 to 2 hours, followed by centrifugation for 15 minutes at 1,100 g and 4°C. Serum aliquots were then transferred to a temperature of −80°C. All samples were jointly stored at the Biobank of Psychiatric Diseases Mannheim (33). We used the following competitive enzyme-linked immunosorbent assays (ELISAs): Progesterone ELISA (RE52231; IBL International GmbH, Hamburg, Germany) and Estradiol ELISA (EIA-2693; DRG Instruments GmbH, Marburg, Germany). In parallel to standard curves on every 96-well plate ranging from 0.15 to 40 ng/mL for progesterone and from 12.5 to 2,000 pg/mL for estradiol, we dispensed duplicates of 25 μL of serum for the progesterone ELISA and 25 μL of serum for the estradiol ELISA. The intra- and interassay coefficients of variation were 3.0% and 10.2% for the progesterone ELISA and 7.0% and 12.9% for the estradiol ELISA, respectively. For the main statistical analyses, we used the progesterone-to-estradiol ratios (progesterone [ng/mL] × 1,000 [pg/ng]) / (estradiol [pg/mL]) of 667 blood samples (72 samples from 49 females: mean=45.0, SD=61.4, range=1.5–334.4; 595 samples from 278 males: mean=12.6, SD=7.5, range=1.5–67.5) (for raw values, see Figures S3–S5 in the online supplement). For additional analyses, we quantified testosterone concentrations (for details on the methods, see the online supplement).

Statistical Analysis

Generalized linear mixed models (here, logistic models) were fitted for "binge drinking day" and "day with any

TABLE 1. Definition of menstrual cycle phases according to cycle length[a]

	Days of Cycle Phases				
Total Cycle Length (days)	Menstrual	Follicular	Ovulatory	Mid-Luteal	Late Luteal
22 (21–23)	1–5	6	7–10	11–17	18–22
25 (24–26)	1–5	6–9	10–13	14–20	21–25
28 (27–29)	1–5	6–12	13–16	17–23	24–28
31 (30–32)	1–5	6–15	16–19	20–26	27–31
34 (33–35)	1–5	6–18	19–22	23–29	30–34

[a] This method for determining menstrual cycle phase takes into account individual differences in cycle length, which are mostly due to variances in the length of the follicular phase.

alcohol use" as binary dependent variables (yes vs. no) with menstrual cycle phase in females or progesterone-to-estradiol ratios in males as predictors (main effects), using a binomial distribution and a logit link function. We report F tests for main effects in the generalized linear mixed models, followed by t tests for the parameter estimates β, indicating differences from the reference category in categorical variables; t values are shown for predictors with three or more categories. The number of AUD criteria fulfilled, weekend days versus weekdays, and COVID-19-related lockdown phase versus no lockdown phase were included in the models, since these variables have been associated with alcohol use (29). Afterward, we tested for differential effects of the menstrual cycle phase or progesterone-to-estradiol ratios by incorporating interaction effects with number of AUD criteria fulfilled and weekend days versus weekdays in the models. We used general linear mixed models to test the effects of menstrual cycle phases (categorical predictor) on the progesterone-to-estradiol ratios (outcome). To account for circadian variations in hormone concentrations, we included the time of blood collection in the mixed models with hormone variables.

To evaluate the robustness of the results and to gain better mechanistic insights, we conducted a range of sensitivity analyses. We used daily amount of alcohol consumption as an additional outcome. Moreover, we analyzed the roles of menstrual cycle day and cycle day squared; mood, social isolation, and responsiveness to alternative rewards; and testosterone, progesterone, and estradiol concentrations (for details, see the supplementary text and Figure S1 in the online supplement).

The multilevel (mixed) models included random intercepts, to account for the nesting structure of each data point within a participant (level 1: e-diary ratings; level 2: participants). Data were analyzed and visualized with SPSS for Windows, version 27.0; SAS, version 9.4; and GraphPad Prism 5. For details on computation of marginal predicted probabilities and standard errors, see the online supplement. Alpha was set at 0.05 (two-sided), without correction for multiple testing.

RESULTS

Sample Characteristics

Participants (N=352 in total; Berlin: N=123; Dresden: N=69; Mannheim: N=160) were allocated to the AUD groups of 74 premenopausal naturally cycling females and 278 males; blood samples from 49 females and 278 males were analyzed (Table 2). The females for whom serum samples were available did not differ significantly in demographic characteristics from those for whom no serum samples were available (see Table S1 in the online supplement).

Females: Lower Binge Drinking Probability and Higher Progesterone-to-Estradiol Ratios in the Late Luteal Versus Other Menstrual Cycle Phases

The probability of binge drinking days and the mean progesterone-to-estradiol ratios changed significantly across the menstrual cycle phases in the group of females (Table 3). The probability of binge drinking days was lower during the late luteal phase (13%) compared with the menstrual (17%), follicular (19%), ovulatory (20%), and mid-luteal phases (17%) (Figure 1) (binge drinking probability vs. late luteal: odds ratio=1.340, 95% CI=1.031, 1.742; odds ratio=1.523, 95% CI=1.190, 1.949; odds ratio=1.683, 95% CI=1.285, 2.206; odds ratio=1.372, 95% CI=1.076, 1.750). As hypothesized, the changes in probability of binge drinking days across the menstrual cycle phases were paralleled by alterations in the mean progesterone-to-estradiol ratios. We found a higher mean ratio during the late luteal phase (mean=95) than during the menstrual (mean=34), follicular (mean=17), and ovulatory phases (mean=24) (difference in progesterone-to-estradiol ratios: −61, 95% CI=−105.492, −16.095; −78, 95% CI=−119.322, −37.039; −71, 95% CI=−114.568, −27.534), and a higher mean ratio during the mid-luteal (mean=73) than during the ovulatory and follicular phases (difference in progesterone-to-estradiol ratios: −49, 95% CI=−86.512, −11.022; −56, 95% CI=−95.045, −16.749) (Table 3; see also Figure S3 and Table S2 in the online supplement). We utilized a quadratic association to determine the cycle day that had the lowest probability of binge drinking and identified this day as being 2.25 days prior to the onset of menses ($f[x]=0.002x^2+0.009x-2.751$; see Figure S6 and Table S3 in the online supplement). The probability of days with any alcohol use did not differ significantly between the menstrual cycle phases; however, the probabilities of binge drinking days and days with any alcohol use were higher on weekend days than on weekdays, and the lockdown phases were associated with a lower probability of days with any alcohol use (Table 3). The interactions of cycle phases with AUD criteria or weekend days

TABLE 2. Demographic, clinical, and alcohol use characteristics of the sample of premenopausal naturally cycling females with AUD and males with AUD[a]

Characteristic or Measure	Females (N=74)		Males (N=278)	
	Mean	SD	Mean	SD
Age (years)	29.7	6.9	37.9	12.7
	N	%	N	%
Marital status				
Single	50	68	126	47
Living in marriage or partnership	19	26	115	43
Living separately	2	3	11	4
Divorced	2	3	13	5
Widowed	1	1	1	0
Employed, past 3 months	64	86	215	81
Highest school qualification				
Pupil at a general education school/in training	3	4	9	3
Secondary general school certificate[b]	0	0	5	2
General certificate of secondary education[c]	10	14	42	16
Advanced technical college certificate[d]	9	12	28	11
General certificate of education[e]	51	69	178	67
Another school degree	1	1	4	2
	Mean	SD	Mean	SD
Progesterone-to-estradiol ratio[f]	45.0	61.4	12.6	7.5
AUD criteria				
Number of criteria met	4.3	1.6	4.0	1.6
	N	%	N	%
Mild AUD (2–3 criteria met)	27	36	121	44
Moderate AUD (4–5 criteria met)	29	39	104	37
Severe AUD (≥6 criteria met)	18	24	53	19
Tobacco smoking, 3-month prevalence	47	64	152	55
Cannabis use, 3-month prevalence	28	38	77	28
	Mean	SD	Mean	SD
e-Diary data on alcohol use (EMA; mean of participants' individual mean values)[g]				
Days with binge drinking (%)	20.9	17.1	29.0	24.6
Weekend days (%)	28.8	20.3	37.5	27.0
Weekdays (%)	14.5	16.7	24.4	25.2
Days with any alcohol use (%)	49.6	22.0	57.3	26.1
Weekend days (%)	58.1	22.6	64.9	27.1
Weekdays (%)	42.7	25.0	52.1	28.4
Daily alcohol use (g/day)	24.8	16.6	39.9	27.3
Weekend days (g/day)	33.1	20.1	50.3	31.5
Weekdays (g/day)	18.4	16.7	32.2	26.0

[a] AUD=alcohol use disorder; EMA=ecological momentary assessment; progesterone-to-estradiol ratio=(progesterone [ng/mL] × 1,000 [pg/ng])/(estradiol [pg/mL]).
[b] Corresponds to "Hauptschulabschluss" in the German educational system.
[c] Corresponds to "Realschulabschluss" or "Abschluss polytechnische Oberschule."
[d] Corresponds to "Fachhochschulreife."
[e] Corresponds to "Abitur."
[f] Number of observations: 72 among 49 females, and 595 among 278 males.
[g] Number of observations: 4,863 among 74 females, and 16,597 among 278 males.

versus weekdays did not reveal significant effects (see Table S4A,B in the online supplement).

To evaluate the robustness of the results, we conducted a range of additional analyses. Similar to the analysis of binge drinking probability, the menstrual cycle phases were significantly related to the daily amount of alcohol consumption (see Table S5 in the online supplement). Since the menstrual cycle has been related to mood, social isolation (34), and responsiveness to reward (35, 36), we investigated the potential influence of these factors on the observed association between cycle phase and binge drinking. The association between cycle phases and probability of binge drinking days was robust against the model adjustments for mood, social isolation, and alternative reward. It was also not significantly moderated by mood, social isolation, or alternative reward (see Table S6A–D in the online supplement). Finally, the number of AUD criteria fulfilled was not significantly associated with the progesterone-to-estradiol

TABLE 3. Multilevel modeling results in premenopausal naturally cycling females with AUD: association of menstrual cycle phases with probability of binge drinking days, days with any alcohol use, and progesterone-to-estradiol ratios estimated in separate models[a]

Variable	β	95% CI	Odds Ratio	t	p	F	df	p
Binge drinking day[b]								
AUD criteria	0.106	−0.050, 0.261	1.111			1.833	1, 69	0.180
Weekend days versus weekdays						104.242	1, 4855	<0.001
Weekend days	0.786	0.635, 0.937	2.195					
Weekdays	[Reference]							
Lockdown versus no lockdown						3.164	1, 4855	0.075
No lockdown	0.364	−0.037, 0.765	1.439					
Lockdown	[Reference]							
Cycle phases						4.154	4, 4855	0.002
Menstrual	0.293	0.031, 0.555	1.340	2.190	0.029			
Follicular	0.420	0.174, 0.667	1.523	3.341	0.001			
Ovulatory	0.521	0.250, 0.791	1.683	3.776	<0.001			
Mid-luteal	0.317	0.074, 0.559	1.372	2.554	0.011			
Late luteal	[Reference]							
Day with any alcohol use[b]								
AUD criteria	−0.022	−0.174, 0.129	0.978			0.087	1, 64	0.769
Weekend days versus weekdays						85.701	1, 4855	<0.001
Weekend days	0.588	0.463, 0.712	1.800					
Weekdays	[Reference]							
Lockdown versus no lockdown						5.718	1, 4855	0.017
No lockdown	0.371	0.067, 0.674	1.449					
Lockdown	[Reference]							
Cycle phases						1.455	4, 4855	0.213
Menstrual	−0.006	−0.210, 0.198	0.994	−0.056	0.955			
Follicular	0.199	0.003, 0.395	1.220	1.988	0.047			
Ovulatory	0.082	−0.135, 0.299	1.086	0.743	0.457			
Mid-luteal	0.104	−0.083, 0.292	1.110	1.091	0.275			
Late luteal	[Reference]							
Progesterone-to-estradiol ratio[c]								
Time of blood collection	4.273	−1.470, 10.016				2.209	1, 65	0.142
Cycle phases						5.407	4, 48	0.001
Menstrual	−60.793	−105.492, −16.095		−2.725	0.009			
Follicular	−78.181	−119.322, −37.039		−3.817	<0.001			
Ovulatory	−71.051	−114.568, −27.534		−3.277	0.002			
Mid-luteal	−22.284	−61.930, 17.363		−1.139	0.262			
Late luteal	[Reference]							

[a] The models include fixed and random intercepts. AUD=alcohol use disorder; β=regression coefficient; progesterone-to-estradiol ratio=(progesterone [ng/mL] × 1,000 [pg/ng])/(estradiol [pg/mL]).
[b] Number of observations: 4,863 among 74 females.
[c] Number of observations: 72 among 49 females.

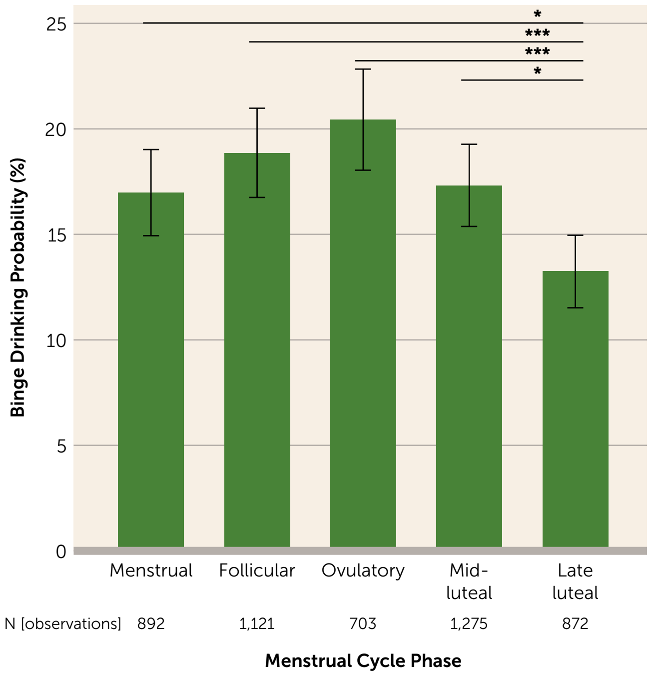
ratio or with progesterone or estradiol concentrations (see Table S7 in the online supplement).

Males: Negative Association Between Progesterone-to-Estradiol Ratios and Alcohol Use Probability

There was a significant association between progesterone-to-estradiol ratios and probabilities of binge drinking days and days with any alcohol use in males with AUD (Table 4; see also Figure S7 in the online supplement). A higher progesterone-to-estradiol ratio was related to lower probabilities of binge drinking days and days with any alcohol use, with a 10-unit increase in the hormone ratio resulting in odds ratios of 0.918 (95% CI=0.843, 0.999) and 0.914 (95% CI=0.845, 0.988), respectively. In general, the probabilities of binge drinking days and days with any alcohol use were significantly higher on weekend days compared with weekdays, and the probability of binge drinking days was significantly affected by the number of AUD criteria fulfilled. The COVID-19 lockdown phases were not significantly related to the probabilities of binge drinking days or days with any alcohol use (Table 4). No significant effects were found in the interactions of the progesterone-to-estradiol ratio with AUD criteria or with weekend days versus weekdays (see Table S8A,B in the online supplement).

Additional analyses showed the progesterone-to-estradiol ratio to be significantly associated with daily amount of alcohol consumption (see Table S9 in the online supplement), which highlights the robustness of the above-reported findings on binge drinking days and days with any alcohol use. After adjustment of the models for testosterone concentrations, the progesterone-to-estradiol ratio was still significantly associated with the probabilities of binge drinking days and days with any alcohol use (see Table S10 in the online supplement). Moreover, fluctuations of the progesterone-to-estradiol ratio over time contributed significantly to the observed effects (see Table S11 in the online supplement). In single-hormone analyses, levels of progesterone, estradiol, and testosterone were not significantly associated with probabilities of binge drinking days or days with any alcohol use (see Tables S12–S14 in the online supplement). The number of AUD criteria fulfilled was also not significantly related to the progesterone-to-estradiol ratio or progesterone or estradiol levels (see Table S15 in the online supplement).

FIGURE 1. Menstrual cycle phase and probability of binge drinking[a]



[a] The graph shows marginal predicted probabilities and standard errors. In premenopausal naturally cycling females with alcohol use disorder (N=74), the probability of binge drinking days varied across the menstrual cycle.
*$p<0.05$. ***$p<0.001$.

DISCUSSION

This study provides novel evidence for the involvement of progesterone relative to estradiol activities in problematic alcohol use in both females and males with AUD. In line with our main hypotheses, we established that in naturally cycling females, a lower probability of binge drinking and higher progesterone-to-estradiol ratios were observed during the late luteal phase in comparison to the menstrual, follicular, and ovulatory phases. In males with AUD, we identified an association of higher progesterone-to-estradiol ratios with lower probabilities of binge drinking and any alcohol use. These findings provide novel insights and support the notion of pharmacologically increasing progesterone relative to estradiol activities to alleviate problematic alcohol use in females and males with AUD.

Martel et al. (17) investigated 22 naturally cycling female university students (ages 18–22 years, binge drinking on 4% of the recorded days) and found a lower likelihood of alcohol drinking in phases of high progesterone relative to estradiol saliva levels. In the present study, we successfully extended this finding to a sample with a broader age range (18–42 years), with AUD, and with a higher probability of binge drinking (21% of the recorded days). Our findings support the notion of a protective effect of progesterone relative to estradiol. However, contrary to our expectations based on the Martel et al. study, we did not observe differential effects of menstrual cycle phases on alcohol use patterns on weekend days and weekdays. This discrepancy may be due to the larger odds ratio in the Martel et al. sample for binge drinking on weekend days compared with weekdays—10.3, compared with 2.2 in our sample—which may be explained by the higher overall binge drinking probability and the older age of our sample as well as the COVID-19 pandemic, with more work in home offices (29).

Females with AUD frequently use alcohol to cope with stress, depression, and anxiety (37, 38), and it is possible that the progesterone-to-estradiol ratio plays a role in this form of self-medication. For example, higher progesterone levels correlate with a lower cortisol stress response following a social stress test during the follicular phase (39). Furthermore, studies with female rats have found that progesterone reduces anxiety-like behavior during nicotine withdrawal (40). A recent review showed pronounced symptoms of mania and depression as well as enhanced alcohol use during the premenstrual and menstrual phases (34), and young social-drinking females were found to consume alcohol to reduce negative affect during their perimenstrual and menstrual phases (8, 41). In line with these findings, we observed an increase in the probability of binge drinking during menses in our sample of relatively older naturally cycling females with AUD. We also found the lowest probability of binge drinking 2.25 days prior to the onset of menses, which might be specific to this population. Since mood per se did not moderate the association between menstrual cycle phases and probability of binge drinking in our study, one might be tempted to speculate that the effects of progesterone relative to estradiol and menstrual cycle on problematic alcohol use interact with individual drinking motives. This proposal should be substantiated in future research endeavors.

The observed changes in probability of binge drinking across the menstrual cycle may guide the development of treatments targeting the specific needs of females with AUD. To the best of our knowledge, menstrual cycle phase–guided

TABLE 4. Multilevel modeling results in males with AUD: association of progesterone-to-estradiol ratios with probability of binge drinking days and days with any alcohol use estimated in separate models[a]

Variable	β	95% CI	Odds Ratio	F	df	p
Binge drinking day[b]						
AUD criteria	0.119	0.007, 0.232	1.127	4.364	1, 228	0.038
Weekend days versus weekdays				418.303	1, 16591	<0.001
Weekend days	0.822	0.743, 0.901	2.275			
Weekdays	[Reference]					
Lockdown versus no lockdown				1.363	1, 16591	0.243
No lockdown	−0.098	−0.263, 0.067	0.907			
Lockdown	[Reference]					
Time of blood collection	−0.002	−0.033, 0.030	0.998	0.013	1, 12410	0.908
Progesterone-to-estradiol ratio	−0.009	−0.017, −0.000	0.991	3.968	1, 16591	0.046
Day with any alcohol use[b]						
AUD criteria	0.007	−0.105, 0.120	1.007	0.017	1, 229	0.897
Weekend days versus weekdays				371.180	1, 16591	<0.001
Weekend days	0.732	0.657, 0.806	2.078			
Weekdays	[Reference]					
Lockdown versus no lockdown				1.011	1, 16591	0.315
No lockdown	−0.080	−0.235, 0.076	0.923			
Lockdown	[Reference]					
Time of blood collection	−0.004	−0.034, 0.026	0.996	0.074	1, 15400	0.786
Progesterone-to-estradiol ratio	−0.009	−0.017, −0.001	0.991	5.088	1, 16591	0.024

[a] The models include fixed and random intercepts. AUD=alcohol use disorder; β=regression coefficient; progesterone-to-estradiol ratio=(progesterone [ng/mL] × 1,000 [pg/ng])/(estradiol [pg/mL]).
[b] Number of observations: 16,597 among 278 males.

intervention studies have been conducted in tobacco use disorder, but are lacking for AUD. For example, smoking cessation has been reported to be more likely to be successful when initiated during the luteal (higher progesterone-to-estradiol ratio) than during the follicular phase (42). Also, initial evidence suggests an added benefit of naltrexone for drinking outcomes during cycle phases with high progesterone-to-estradiol ratios in premenopausal female heavy-drinking smokers (43). Thus, cycle phase–sensitive ecological momentary interventions and hormone therapies promise to yield significant advancements in AUD research.

In males with AUD, we identified an association of higher progesterone-to-estradiol ratios with lower probabilities of binge drinking and any alcohol use, although the effect size (odds ratio) was relatively small. Consistent with this finding, a previous study reported higher estradiol blood levels in males with AUD compared with control subjects (44). Moreover, a placebo-controlled study in cocaine-dependent individuals demonstrated that administering progesterone reduces cue-induced craving and cortisol response, with no significant differential medication effect between males and females (13). Safety measures indicated that progesterone was well tolerated (13), despite the lower overall progesterone blood concentrations in males relative to premenopausal naturally cycling females. Taken together, these findings highlight the potential role of progesterone relative to estradiol as a treatment target for AUD in males as well.

For decades, gestagen and estrogen modulators have been used for various reasons, and preliminary study results indicate that progesterone treatment may be well tolerated and safe in females and males with cocaine use disorder (13; see also reference 25 for adverse effects). Progesterone acts together with its metabolites in the neurosteroidal pregnenolone-progesterone-allopregnanolone pathway. The pathway was found to be involved in GABAergic as well as endocannabinoid signaling, to be altered by alcohol intoxication, and to be disrupted in AUD and other stress-related disorders, highlighting its promising potential as a future treatment target (45–47). Moreover, previous studies have established pharmacological (e.g., gamma-hydroxybutyric acid [48, 49]) and behavioral (e.g., social closeness [50]) interventions to increase progesterone. Hence, this study's results inform the development of novel treatment approaches for females and males with AUD.

Our study had several notable strengths. First, we investigated a large sample of females and males with mainly mild to moderate AUD across a broad age range. Second, we used daily reports of alcohol use (assessed every other day), which minimizes recall bias and provides ecologically more valid results than data assessed retrospectively via the timeline followback method (20, 51, 52). We employed advanced smartphone-based EMA technology across a 12-month period with sound adherence rates (69% and 66% of queries on alcohol use answered in females and males, respectively), resulting in two large, real-time, intensively sampled longitudinal data sets (21,460 smartphone entries) that enabled hierarchical repeated-measures analyses and ecologically valid findings (53). Third, we used a standardized and established definition of menstrual cycle phases based on unambiguous hormonal events (32) and verified the cycle phase classifications by quantifying serum levels of progesterone and estradiol. Fourth, we showed that the findings of this study are robust against the adjustment for COVID-19 lockdown phases; however, the lack of data on COVID-19 infections or vaccinations precluded us from testing their potential specific effects (54, 55).

Our study also had certain limitations. First, the study design included only four blood drawings during the 12-month period, restricting the number of available serum samples and hormone values. Because of the low number of blood samples from females, we were not able to directly analyze the association between progesterone-to-estradiol ratio and problematic alcohol use in the female sample and instead used the menstrual cycle as a proxy measure. In addition, the limited number of females in the study (N=74) may have led to spurious or nongeneralizable findings. Second, although self-reported alcohol use assessed via EMA is more reliable than retrospective assessments (20, 51, 52), it does not necessarily translate to blood alcohol concentrations. Third, our sample included mainly persons of Central European descent, and thus our analysis does not address effects of social exclusion stress on sex hormones or biological variation among different populations worldwide. Fourth, the observational character of our study does not allow for interpretations of directionality and underlying causality, and moreover, several variables vary on a time scale similar to that of the menstrual cycle. However, since we found no evidence that the observed variations of the progesterone-to-estradiol ratio across the menstrual cycle in females with AUD differed from those expected in healthy females, and since the number of AUD criteria fulfilled was not significantly related to the hormone measures in either females or males with AUD, we are tempted to speculate that the effects observed are in favor of hormonal variations influencing alcohol use. To obtain better insights into the directionality and to demonstrate causality underlying the associations of menstrual cycle and progesterone-to-estradiol ratio with binge drinking and any alcohol use, further translational experiments using progesterone and estradiol manipulations are needed as a critical next step in this research field.

CONCLUSIONS

We demonstrated a lower probability of binge drinking in females during the late luteal phase (with higher progesterone-to-estradiol ratios) compared with the menstrual, follicular, and ovulatory cycle phases. Similarly, we observed lower probabilities of binge drinking and any alcohol use in males in phases of higher progesterone-to-estradiol ratios. These findings indicate that the administration of progesterone to females and males with AUD may have the potential to reduce problematic alcohol use. Moreover, the results suggest that menstrual cycle phase–dependent strategies can be beneficial in females with AUD.

Future studies need to identify how drinking motives, brain (re)activities to alcohol cue exposure (e.g., of the reward system), incentive delay, and affective neural processing are involved in the relationships observed here. They should also control for potential effects of premenstrual disorders and investigate different ethnicities. The recruitment of high numbers of naturally cycling females not taking oral contraceptives can be challenging. However, this study's findings highlight the pressing need to balance females and males in future projects to counteract the sex imbalance in AUD research.

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Examination Questions for "Associations of Menstrual Cycle and Progesterone-to-Estradiol Ratio With Alcohol Consumption in Alcohol Use Disorder: A Sex-Separated Multicenter Longitudinal Study"

1. **In the female sample, predicted probability of binge drinking days changed across the menstrual cycle. During which phase of the cycle does the probability of binge drinking days reach its lowest point?**
   A. Menstrual phase
   B. Follicular phase
   C. Ovulatory phase
   D. Late luteal phase
2. **Which of the following statements about the observed association between the menstrual cycle and the probability of binge drinking days in the female sample is correct?**
   A. Social isolation was identified as a significant moderator of the observed association
   B. The interaction of cycle phases with number of AUD criteria fulfilled was not significantly related to probability of binge drinking days
   C. Mood moderated significantly the observed association
   D. The cycle day with the lowest probability of binge drinking was determined eleven days prior to the onset of menses
3. **Higher progesterone-to-estradiol ratios in blood of the male sample were related to lower probabilities of binge drinking days and days with any alcohol use. Which of the following statements about these associations is supported by the results of the study?**
   A. Longitudinal changes in the progesterone-to-estradiol ratio contributed significantly to the observed associations
   B. In single hormone analyses, estradiol concentrations were significantly associated with probabilities of binge drinking days and days with any alcohol use
   C. The observed associations are a consequence of significant differences between lockdown periods and periods without lockdown due to COVID-19
   D. The observed associations did not remain significant after adjusting the models for testosterone concentrations