

The cortisol levels in the follicular and luteal phases of the healthy menstruating women: a meta-analysis

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Abstract. – OBJECTIVE: The conflicting results of the previous studies regarding the serum cortisol through the menstrual cycle warranted further research. We aimed to detect the cortisol levels in the follicular and luteal phases of healthy menstruating women.

MATERIALS AND METHODS: A literature search was conducted by two independent authors according to PRISMA criteria over PubMed, Web of Science and Psych-Info to retrieve the articles published in English from 1990 until 2020 and containing the keywords, Cortisol, Menstrual, Follicular, or Luteal. The quality assessment of the articles/studies was done using the CONSORT and STROBE checklists. The risk bias was assessed by two independent authors using Cochrane risk-bias assessment tool.

RESULTS: Twenty-eight (28) articles were included in this meta-analysis. The cortisol levels were significantly higher in the studied-participants' follicular phase compared to the luteal phase ($p < 0.01$). The cortisol levels sub-analysis showed a significant effect of plasma cortisol over the salivary cortisol ($p = 0.04$). The cortisol assay time showed a significant effect of the morning cortisol over the afternoon cortisol ($p = 0.005$).

CONCLUSIONS: This meta-analysis found the cortisol levels were significantly higher in the studied-participants follicular phase compared to the luteal phase. The cortisol sub-analysis showed a significant effect of plasma and morning cortisol over the salivary and afternoon cortisol, respectively.

Key Words:

Cortisol, Follicular, Luteal, Menstrual cycles, Meta-analysis.

Introduction

Cortisol is a non-cyclic hormone that plays an important role in glucose metabolism, maintaining vascular tone, regulating the immune response, and in the body's response to stress. The serum cortisol has a clear daily rhythm, the maximum level of cortisol is at 8 AM in the morning, while the minimum cortisol level is at 10-11 PM in the evening¹. Stress always provokes high cortisol secretion, which can suppress the hormones responsible for ovulation and menstruation².

Women are exposed to major depressive disorder (MDD), stress, and anxiety spectrum disorders¹⁻⁹, especially at puberty, pre-menstrual, postpartum, and at menopause, which suggests a link between the sex hormones and cortisol¹.

Previous studies^{8,9} found that serum cortisol was higher in the menstrual cycle's luteal phase than the follicular phase. While other studies^{10,11} reported similar serum cortisol levels in menstrual cycle phases.

The conflicting results of the previous studies¹²⁻¹⁴ regarding the serum cortisol through the menstrual cycle warranted further research.

Therefore, this meta-analysis was conducted to detect the cortisol levels in the follicular and luteal phases of healthy menstruating women.

Materials and Methods

Research Strategy

A literature search was conducted by two independent authors (I.A. Abdelazim and I.I. Samaha)

according to PRISMA criteria¹⁵ over PubMed, Web of Science, and Psych-Info to retrieve the articles published in English from 1990 until 2020 and containing the keywords, Cortisol, Menstrual, Follicular, or Luteal.

Inclusion Criteria

Studies published between 1990 and 2020 including baseline data such as stress and/or exercise before collections of samples for laboratory evaluation, studies including collections of samples across the menstrual cycle (follicular and luteal phases) and evaluating disease in healthy menstruating women compared to placebo and/or controls were included in this meta-analysis.

Exclusion Criteria

After reviewing the abstracts, review, case reports, animal studies, studies including male subjects only, one menstrual phase, evaluating diseased women, stress, pregnant, peri/post-menopausal or smoking women or women using hormonal contraceptives, menstrual phases-specific procedure (i.e., IVF), written in languages other than English, without controls or did not mention the cortisol assay (i.e., serum, urinary or salivary) were excluded from this meta-analysis.

After reviewing the full articles, studies that did not include healthy controls, two menstrual phases evaluation or cortisol assay, or the exact time of sample collections for cortisol assay were also excluded from this meta-analysis.

Quality Assessment

The quality assessment of the articles/studies was done using the CONSORT and STROBE checklists.

The CONSORT checklist is a 25-item checklist, focusing on the article/study design, analysis, and interpretation. The STROBE checklist is a 22-item checklist, evaluating different sections/parts of the observational studies.

The Risk Bias

The risk for bias was assessed by two independent authors (I.A. Abdelazim and I.I. Samaha) using the Cochrane risk-bias assessment tool, which includes selection bias, performance bias, detection bias, attrition bias, and reporting bias.

Data Extraction

The following data were extracted; age, body mass index (BMI), the time and the menstrual day of cortisol assay either in the follicular or in the luteal phase, studies reporting multiple cortical

assays across the menstrual cycle (the cortisol level at day-1 of the menses was considered the follicular phase cortisol and the cortisol level in day-21 of the menses was considered the luteal phase cortisol).

The morning cortisol was considered when multiple cortisol assays across the day were done, and the serum cortisol was considered when multiple sources of cortisol (i.e., salivary and blood) were reported.

Statistical Analysis

Analysis of data was carried out by calculating the Cohen's-d effect size (the mean and variance values were provided for groups of women in follicular and luteal phases, then the mean difference between the two groups was divided by the pooled standard deviation). Then, the J-correction factor was done to obtain the Hedges' g effect size^{16,17}. The studies' heterogeneity was assessed using the Q-statistic test with its *p*-value. *p*<0.05 was considered significant.

The groups' sub-analysis was completed according to the source (serum vs. saliva) and time of cortisol assay (morning vs. afternoon).

Results

PRISMA Chart (Figure 1) shows the number of articles identified, screened, causes of exclusion, the number of full articles reviewed, and the final number of articles (28) included in this meta-analysis.

Most of the studied participants were 20 years old, their BMI was <25 Kg/m², and reported the follicular phase of the menstrual cycle from day 1 to day 14 and the luteal phase of the menstrual cycle from day 15 to day 28.

Estrogen was evaluated as the main follicular phase hormone, and progesterone as the main luteal phase hormone.

Other studies in the literature identified the luteal phase after the ovulation [i.e., ovulation either detected by the luteinizing hormone (LH) surge or the rising basal body temperature or by the pelvic ultrasound].

The cortisol was evaluated either in serum/plasma, urine, or saliva and either morning, afternoon, or over several hours (Table I).

Evaluation of Cortisol Standard Mean Across the Menstrual Cycle

The cortisol levels were significantly higher in the studied-participants' follicular phase compared to the luteal phase (Hedges' g=0.13; *p*<0.01), (Table II and Figure 2).

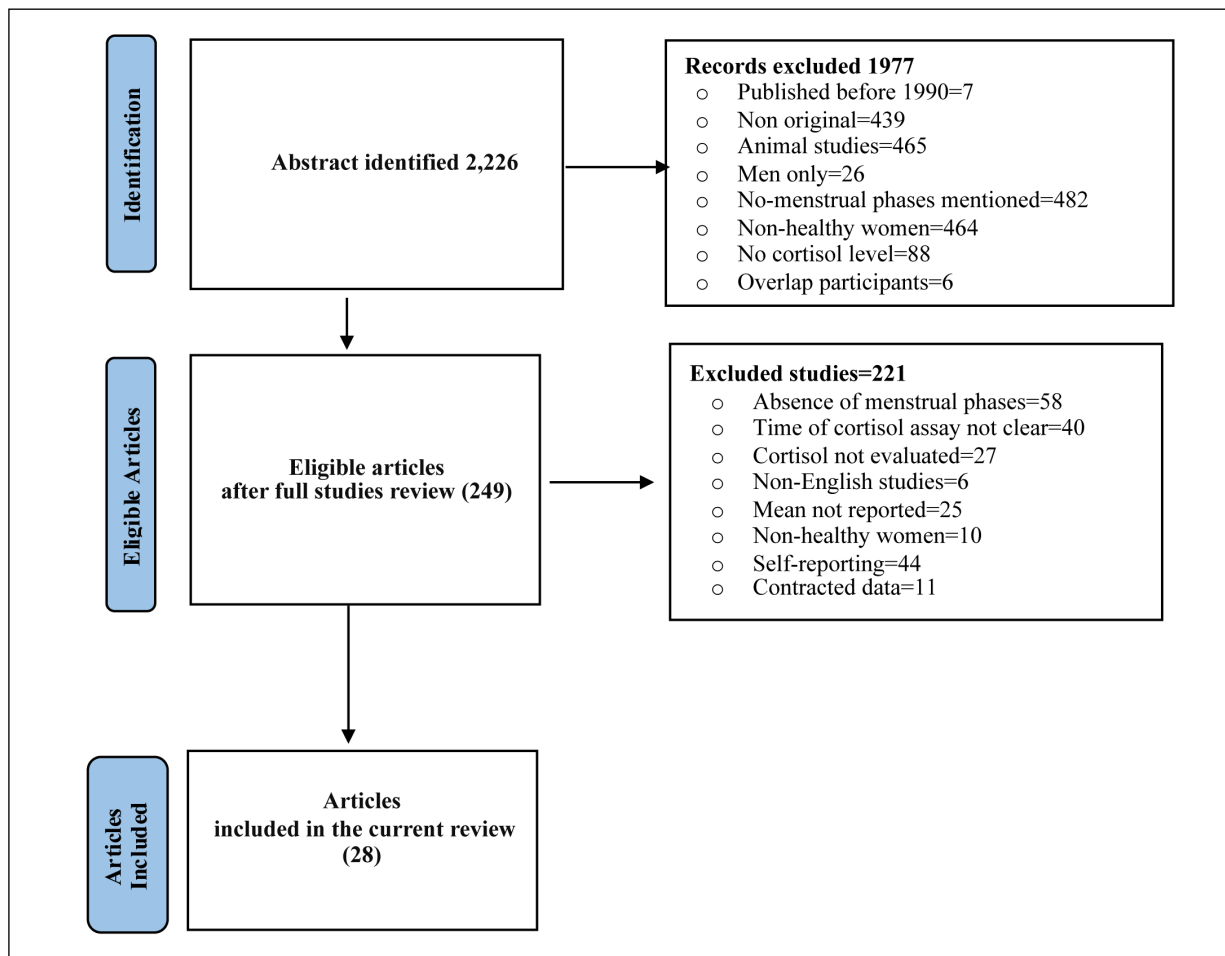


Figure 1. The PRISMA flow chart.

The Cortisol Levels Sub-Analysis Based on the Cortisol Source and Assay Time

The cortisol levels sub-analysis showed a significant effect of plasma cortisol over salivary cortisol ($p=0.04$). The cortisol assay time showed a significant effect of the morning cortisol over the afternoon cortisol ($p=0.005$), (Table III).

Discussion

Previous studies^{8,9} found that serum cortisol was higher in the luteal phase of the menstrual cycle compared to the follicular phase. While other studies^{10,11} reported similar serum cortisol levels in menstrual cycle phases.

The conflicting results of the previous studies¹²⁻¹⁴ regarding the serum cortisol through the menstrual cycle warranted further research.

Therefore, a literature search was conducted over PubMed, Web of Science, and Psych-Info

and 28 articles^{8-11,18-41} published in English from 1990 until 2020, containing the keywords, Cortisol, Menstrual, Follicular, or Luteal were included in this meta-analysis to detect the cortisol levels in the follicular and luteal phases of the healthy menstruating women.

This meta-analysis found that cortisol levels were significantly higher in the studied participants' follicular phase compared to the luteal phase ($p<0.01$).

The hypothalamus paraventricular nucleus (PVN) releases the corticotropin-releasing hormone (CRH), through the hypophyseal portal axis, which stimulates the synthesis of adrenocorticotrophic hormone (ACTH) from the anterior pituitary.

The ACTH stimulates cortisol synthesis from the adrenal gland². The PVN neurons express estrogen receptor beta (ER- β) and estrogen receptor alpha (ER- α)⁴².

Estradiol has an equal affinity to both types of estrogen receptors in the PVN and can stimulate or inhibit the hypothalamo-pituitary axis (HPA).

Table 1. Characteristics of the studied participants, menstrual phases, hormones evaluated, time and source of the cortisol evaluated.

Article/Publication year	Sample Size		Mean Age	Mean BMI	Menstrual phase			Cortisol	
	Follicular phase	Luteal phase			Follicular phase	Luteal phase	Hormones evaluated	Time	Source
Andreano et al ¹⁸ 2008	20	24	-	-	1-7	18-24	E & P	Afternoon	Saliva
Hoeger Bement et al ¹⁹ 2009	20	20	20.9	23.0	Mid	Mid	LH	Afternoon	Saliva
Bricout et al ²⁰ 2003	11	11	25.5	19.9	Mid	Mid	E & P	24-hours	Urine
Cannon et al ²¹ 1998	7	8	-	-	1-14	15-28	P	24-hours	Urine
Caufriez et al ²² 2018	10	10	30.0	21.8	3-8	23-28	Basal Temp.	24-hours	Urine
Childs et al ²³ 2010	29	23	21.9	22.3	3-10	16-24	LH	Morning	Plasma/saliva
Espin et al ⁸ 2013	30	30	19.3	21.7	5-8	20-24	Basal Temp.	Afternoon	Saliva
Heitkemper et al ²⁴ 1996	25	25	33.1	23.6	1-7	15-22	LH	Morning/afternoon	Urine
Huang et al ²⁵ 2015	18	18	22.0	20.0	1-4	24-28	E & P	Afternoon	Saliva
Inoue et al ¹¹ 2007	9	9	23.7	-	1-14	21-28	E & P	Morning	Plasma
Judd et al ²⁶ 1995	6	6	-	-	3-5	20-24	LH	10-hours	Serum
Kasa-Vubu et al ²⁷ 2005	10	14	29.4	24.0	1-14	15-28	LH & P	24-hours	Plasma
Kerdelhué et al ²⁸ 2001	11	11	-	-	1	21	LH	Morning	Serum
Kirschbaum et al ²⁹ 1999	19	21	23.4	21.7	4-7	21-25	E & P	Afternoon	Plasma/saliva
LeRoux et al ³⁰ 2014	9	9	21.8	22.5	8-10	20-22	E & P	Morning/afternoon	Saliva
Lombardi et al ³¹ 2004	20	20	26.2	-	5-7	22-26	LH & P	Morning	Serum
Maki et al ³² 2015	20	20	27.0	25.0	2-4	22-24	LH	Afternoon	Saliva
Ohara et al ³³ 2015	7	7	22.3	20.5	1-14	15-28	LH	Morning	Saliva
Paoletti et al ³⁴ 2006	14	14	31.5	24.2	5-8	21-24	Basal Temp.	Morning	Serum
Parry et al ³⁵ 2000	30	30	37.2	-	6-8	26-28	LH	Morning	Plasma
Rasgon et al ³⁶ 2000	5	5	27.0	-	2-9	7-14	LH	Morning	Plasma
Reynolds et al ³⁷ 2018	61	61	21.7	-	7-10	20-23	LH	Afternoon	Saliva
Roche and King ³⁸ 2015	23	23	24.2	23.6	1-14	15-28	E & P	Morning	Plasma
Stewart et al ³⁹ 1993	4	4	24.6	24.7	7	21	P	12-hours	Plasma
Su et al ⁴⁰ 1997	10	10	30.8	-	3-7	21	P	Morning	Plasma
Timon et al ¹⁰ 2013	20	20	-	21.3	1-2	21-22	Basal Temp.	Morning	Urine
Villada et al ⁹ 2017	13	17	19.0	21.3	5-8	20-24	Basal Temp.	Afternoon	Saliva
Wolfram et al ⁴¹ 2011	29	29	26.3	22.1	2-6	21-24	LH	-	Saliva

BMI: Body mass index. E: Estrogen, LH: Luteinizing hormone. P: Progesterone. Temp. Temperature

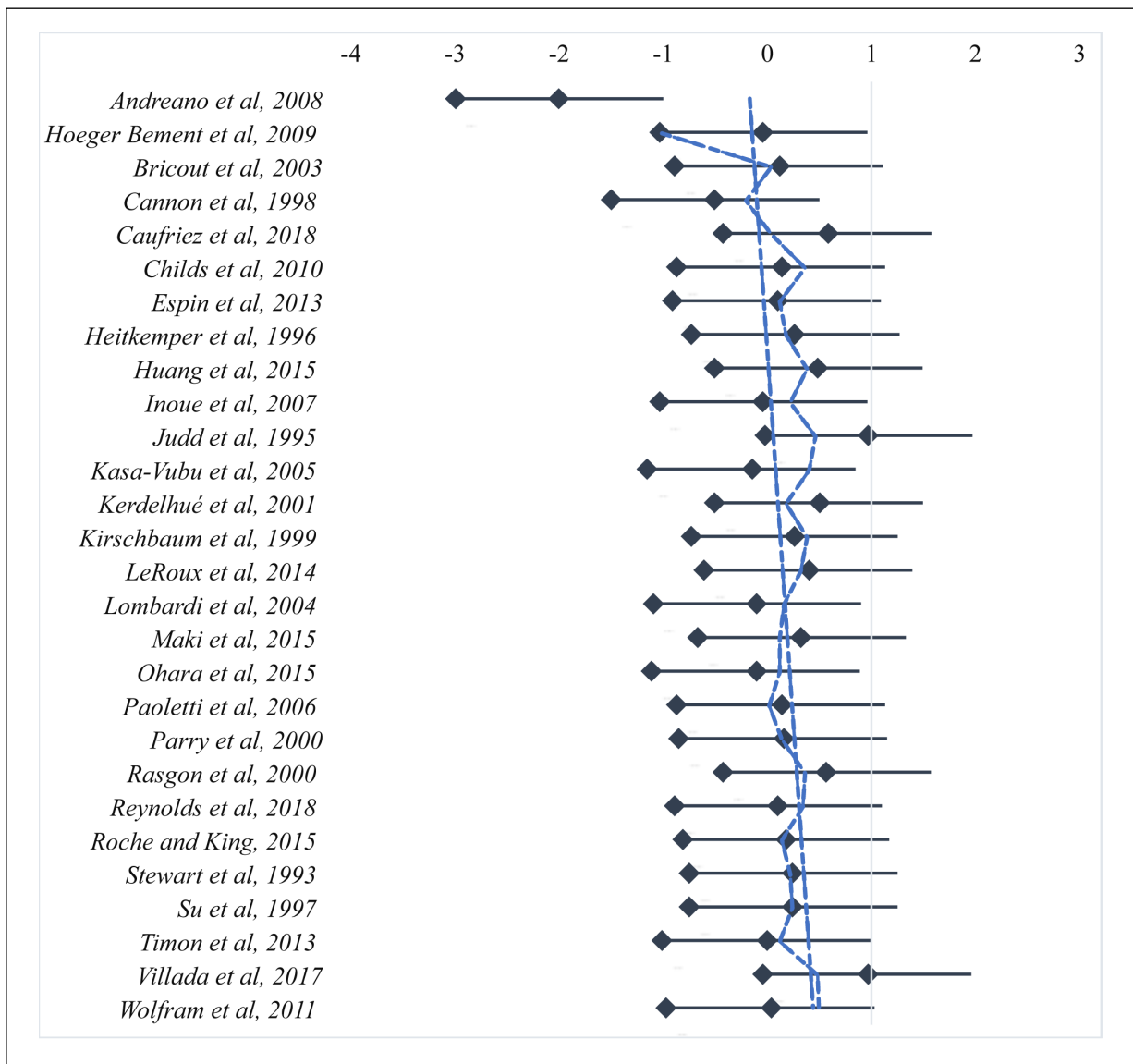


Figure 2. Forest plot of the cortisol across the menstrual cycle.

The estradiol stimulation for the ER- β receptors leads to a reduction of cortisol levels, while the estradiol stimulation for the ER- α receptors leads to increased cortisol levels⁴³.

Therefore, in the luteal phase, when the estradiol is high compared to the early/mid follicular phase, the estradiol can either decrease or increase the circulating cortisol depending on the extent of ER- β or ER- α stimulation and inhibition².

Pregnanolone is a potent progesterone secreted during the luteal phase of the menstrual cycle, which exerts an inhibitory effect on the gamma-aminobutyric acid (GABA)A receptor in the PVN with subsequent inhibition of the HPA and decrease of the circulating cortisol^{44,45}.

Therefore, under normal physiological conditions, the higher luteal phase progesterone modulates the (GABA)A receptor with a subsequent decrease in the circulating cortisol. However, De Sio et al⁴⁶ found that urinary cortisol was linked to work-related stress (WRS), and gender and was a non-invasive indicator for WRS.

This cortisol levels sub-analysis in this meta-analysis showed a significant effect of plasma cortisol over salivary cortisol ($p=0.04$). The cortisol assay time showed a significant effect of morning cortisol over afternoon cortisol ($p=0.005$).

Normally, >80% of the circulating cortisol is bound to corticosteroid-binding globulin (CBG) and <5% of the circulating cortisol is free in

Table II. The standardized mean difference and confidence interval of the cortisol across the menstrual cycle.

Article/Publication year	Standardized Mean Difference of cortisol (SMD)	Negative Confidence Interval (CI-)	Positive Confidence Interval (CI+)
Andreano et al ¹⁸ 2008	-2.0	-0.80	0.39
Hoeger Bement et al ¹⁹ 2009	-0.04	-0.38	0.30
Bricout et al ²⁰ 2003	0.11	-0.35	0.57
Cannon et al ²¹ 1998	-0.50	-1.53	0.53
Caufriez et al ²² 2018	0.58	0.04	1.12
Childs et al ²³ 2010	0.13	-0.42	0.68
Espin et al ⁸ 2013	0.09	-0.42	0.60
Heitkemper et al ²⁴ 1996	0.27	-0.04	0.59
Huang et al ²⁵ 2015	0.49	-0.17	1.15
Inoue et al ¹¹ 2007	-0.04	-0.54	0.47
Judd et al ²⁶ 1995	0.97	-0.23	2.16
Kasa-Vubu et al ²⁷ 2005	-0.15	-0.96	0.66
Kerdelhué et al ²⁸ 2001	0.50	-0.00	1.00
Kirschbaum et al ²⁹ 1999	0.26	-0.37	0.88
LeRoux et al ³⁰ 2014	0.40	-0.53	1.33
Lombardi et al ³¹ 2004	-0.10	-0.44	0.24
Maki et al ³² 2015	0.33	-0.29	0.96
Ohara et al ³³ 2015	-0.11	-0.68	0.47
Paoletti et al ³⁴ 2006	0.13	-0.28	0.54
Parry et al ³⁵ 2000	0.15	-0.13	0.43
Rasgon et al ³⁶ 2000	0.57	-0.20	1.34
Reynolds et al ³⁷ 2018	0.10	-0.10	0.29
Roche and King ³⁸ 2015	0.18	-0.40	0.75
Stewart et al ³⁹ 1993	0.25	-0.52	1.03
Su et al ⁴⁰ 1997	0.25	-0.74	0.24
Timon et al ¹⁰ 2013	-0.01	-0.35	0.33
Villada et al ⁹ 2017	0.96	0.20	1.73
Wolfram et al ⁴¹ 2011	0.03	-0.25	0.31

Table III. The cortisol levels sub-analysis based on the cortisol source and assay time.

Variables	Standard Mean difference (SMD)				Q-statistic test			
	Mean	Standard Error (SE)	z-value	p-value	Confidence Interval (CI)	Degrees of freedom (DF)	Value	p-value
Plasma	0.12	0.058	2.09	0.04*	0.008-0.24	18	13.2	0.78
Saliva	0.118	0.062	1.92	0.055	-0.003-0.24	8	7.87	0.45
Morning	0.136	0.049	2.81	0.005*	0.04-0.23	21	16.7	0.73
Afternoon	0.097	0.072	1.35	0.18	-0.044-0.24	7	9.16	0.24

blood². The CBG is synthesized by the liver, and it is regulated by estradiol².

The plasma cortisol reflects the total cortisol, while the salivary cortisol reflects the free cortisol. The changes in the circulating CBG have a significant effect on the total cortisol, but not on the free cortisol concentration².

The ethinyl estradiol-containing contraceptive pills increase the CBG and decrease the circulating free cortisol.

Nenke et al⁴⁷ found that the CBG elevated in pregnancy and during the use of ethinyl estra-

diol-containing contraceptives with subsequent decreased free cortisol.

This meta-analysis did not account for the changes in the CBG across the menstrual cycle phases. The changes in the CBG across the menstrual cycle phases due to changes in estradiol levels warrant further studies⁴⁸.

The self-reported phases of the menstrual cycle and the rough evaluation of follicular vs. luteal cortisol rather than early/mid follicular vs. early/mid luteal cortisol in the included articles are the main limitations of this meta-analysis.

Further studies evaluating the early/mid follicular vs. early/mid luteal cortisol are needed rather than the rough evaluation of follicular vs. luteal cortisol to understand the women's rhythmic hormonal changes.

Conclusions

This meta-analysis found that cortisol levels were significantly higher in the studied-participants' follicular phase compared to the luteal phase. The cortisol sub-analysis showed a significant effect of plasma and morning cortisol over the salivary and afternoon cortisol, respectively.

Conflict of Interest

The authors declare that they have no conflict of interest.

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None.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

DK, AT, AD, and AA are responsible for the study concept and design, literature review, quality assessment, data collection and final revision before submission for publication. IAA, SS, ES and IIS are responsible for literature review, risk bias assessment, Microsoft editing and final revision before submission for publication. AO, FB, GI, KB and TB are responsible for literature review, update of the references and final revision before submission for publication. All the authors have read and agreed to the published version of the manuscript.

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