Meta-Analysis the Effect of Obesity and Stress on Menstrual Cycle Disorder

Lutfi Annarahayu[1], Yulia Lanti Retno Dewi[2], Rita Benya Adriyani[3]

[1]Master's Program in Public Health,Universitas Sebelas Maret
[2]Faculty of Medicine,Universitas Sebelas Maret
[3]Health Polytechnics, Ministry of Health Surakarta

ABSTRACT

Background: There are many factors that influence menstrual patterns to become irregular, including stress and obesity. Menstrual cycle irregularities can have a serious impact on women's health, which will affect the metabolic, fertility, sexual and reproductive systems. This study aims to analyze the influence of obesity and stress on menstrual cycle disorders with a meta-analysis study.

Subjects and Method: This study is a systematic study and meta-analysis, with the following PICO, Population= women of childbearing age. Intervention= obesity and stress. Comparison = not obese and not stressed. Outcome = disruption of the menstrual cycle. The articles used in this study were obtained from several databases, including PubMed, ScienceDirect and Google Scholar. The keywords used are "menstrual disorder and obesity and stress", "obesity and menstrual irregularity", "obesity OR stress AND menstrual irregularity OR cross sectional study". The articles included in this study are full text articles with a cross sectional study design. Articles were collected using PRISMA flow diagrams. Articles were analyzed using the Review Manager 5.3 application.

Results: Meta-analysis of 8 observational studies showed that obese women were 4 times more likely to have menstrual cycle disorders than normal weight (aOR= 4.19; 95% CI= 1.99 to 8.84; p= 0.002). Meta-analysis of 6 observational studies showed that women with stress had a risk of experiencing menstrual cycle disorders 1.28 times compared to women who did not experience stress (aOR= 1.28; 95% CI= 1.13 to 1.45; p = 0.001).

Conclusion: Obesity and stress affect menstrual cycle disorders.

Keywords: obesity, stress, menstrual cycle disorders, meta-analysis

Correspondence:
Lutfi Annarahayu. Master's Program in Public Health, Universitas Sebelas Maret. Jl. Ir. Sutami 36A, Surakarta 57126, Central Java. Email: Lutfi.annarahayu@student.uns.ac.id. Mobile: 081910979054.

BACKGROUND

Menstruation is a complex process involving several hormones, sexual organs and the nervous system. Hormones have an important influence on menstruation, if the hormones are not balanced then the cycle will be disrupted. The menstrual cycle is a clinical sign of female reproductive function (Diaz et al., 2006). Menstrual cycle length is known as a predictor of health such as breast cancer and cardiovascular risk factors (Chavez and MacGregor et al., 2005).

There are many factors that influence menstrual patterns to become irregular, including stress, hormonal imbalance, thyroid disorders, obesity or weight gain, polycystic ovary disease, diabetes, metabolic syndrome, medication, environment, behavior and lifestyle factors. Irregularities in the menstrual cycle can seriously impact a woman's immediate and long-term health causing disturbing symptoms that affect metabolism, sleep, fertility, sexuality, reproductive life, and more (Sommer et al., 2017; Ganesan et al., 2019) .

Abnormal menstrual cycles are also associated with decreased fertility. The distance of the menstrual cycle is different for each woman, generally ranging from 15-45 days with an average of 28 days and the duration ranging from 2-8 days, an average of 4-6 days with blood released ranging from 60-80 ml per cycle (Prathita et al., 2017). Disorders of the menstrual cycle or irregularities are a major gynecological problem among women, especially adolescents and a source of anxiety for them and their families (Ali Abdella et al., 2016). According to a report by the World Health Organization (WHO), the prevalence of menstrual cycle disorders in women is around 45% (2012). A survey reported that about 64% of girls had at least one problem related to menstruation (Nath and Garg, 2008). The prevalence of menstrual disorders in India was recorded at 87%. Various types of menstrual disorders include menstrual irregularities, menorrhagia, polimenorrhea, oligomenorrhea, dysmenorrhea, and others (Campbell and McGrath, 1997).

A person is said to be obese if he has a BMI >30 kg/m² (WHO, 2020). Obesity is a serious public health problem worldwide because obesity plays a role in increasing morbidity and mortality. In 2016 more than 1.9 billion adults aged >18 years were overweight and >650 million of them were obese. The percentage of adolescents aged 12-19 years who are obese increased from 5% to 21% in 1975-2016. More than 340 million children and adolescents aged 5-19 years were overweight or obese in 2016. The percentage of obese children and adolescents with female gender was 6% and male was 8% (WHO, 2020).

WHO data in 2016, globally there are about 35 million people who experience depression, 60 million people with bipolar disorder, 21 million people with schizophrenia, and 47.5 million people with dementia. The results of the 2018 Basic Health Research show that the prevalence of mental disorders as indicated by symptoms of depression at the age of 15 years and over reaches 6.1% (Ministry of Health of the Republic of Indonesia, 2019a).

Based on an analysis of 22 studies involving 144,000 participants, it was found that obese adolescent girls were 44% more likely to develop depression or be diagnosed with depression in the future (Ministry of Health, 2019b). Stress levels can interfere with reproductive function which will stimulate the hypothalamus to release the hormone CRH which works antagonistically with GnRH so that GnRH levels decrease which causes disruption of the menstrual cycle (Sari and Setiarini, 2013).

Based on the high incidence of menstrual cycle disorders, obesity and stress experienced by women at this time, the researchers are interested in studying the effect of obesity, stress on menstrual cycle disorders. Researchers used a systematic review approach to relevant studies using meta-analysis to clearly identify the magnitude of the influence of obesity and stress on menstrual cycle disorders.

SUBJECTS AND METHOD

1. Study Design

The study design used in this research is a systematic review and meta-analysis, using PRISMA flow diagram guidelines. Article searches were conducted using journal databases including: PubMed, Google Scholar and Science Direct. The keywords used are "menstrual disorder", "menstrual disorder and obesity and stress", "obesity and menstrual irregularity", "stress and menstrual disorder", "obesity or stress or menstrual irregularity or cross sectional study", "obesity or stress or menstrual disorder or adjusted odd ratio".

2. Inclusion Criteria

In this study, the inclusion criteria were articles that used an observational study design, namely cross-sectional, articles in English, the analysis used was multivariate with adjusted odds ratio, the research subjects were women of childbearing age, the intervention was obesity and stress and the outcome was impaired menstrual cycle.

3. Exclusion Criteria

Exclusion criteria in this study include articles published not in full text before 2000 and in languages other than English.

4. Operational Definition of Variable

In formulating research problems, PICO is used. Population is women of childbearing age. Intervention is obesity and stress, with comparison that is not obesity and not stress and outcomes are menstrual cycle disorders

Menstrual cycle is periodic and cyclic bleeding originating from the uterus that is physiological in nature accompanied by the shedding of the endometrial wall that occurs in women of reproductive age

Obesity is a very high accumulation of fat in the body. Characterized by BMI values > 30kg/m2

Stress. The body's reaction/response to psychosocial stressors (mental stresses/life burdens).

5. Research Instrument

An assessment of the quality of research articles was carried out using the Critical Appraisal Checklist for Cross Sectional Study from the Center for Evidence Based Management (2014).

6. Data Analysis

The Review Manager application (RevMen 5.3) was used in analyzing the data in this study. The results of data analysis are in the form of effect size values and study heterogeneity which later on the results of the analyzed data are interpreted in the form of forest plots and funnel plots.

RESULTS

The process of searching for articles by searching through databases with journals can be seen in Figure 1. There were 1278 articles identified from the databased, after the deletion process of published articles, 184 articles were found with 130 of them eligible for a full text review. Articles were excluded for several reasons, so that 14 articles were included in the synthesis and meta-analysis studies.

Research from primary studies related to the effect of obesity and stress on menstrual cycle disorders consists of 14 studies originating from 9 studies from the Asian continent, 4 studies from the European continent, and 1 study from the Australian continent.

| Articles identified through database search(n= 1,278) | → | Added articles identified from other searches (n= 1) |

| Delete duplicate data (n=437) | | Articles issued (n= 712) 1. Irrelevant title (206) 2. Not an original article (198) 3. Non-Cross-Sectional (270) 4. Does not speak English (14) 5. Not Full Text (24) |

| Filtered articles (n=842) | → | |

| Full-text articles that are eligible(n= 130) | → | Full-text published articles (n=116) 1. Inappropriate intervention (42) 2. Inappropriate outcome (63) 3. Population does not match (11) |

| Articles included in the qualitative synthesis (n=14) |

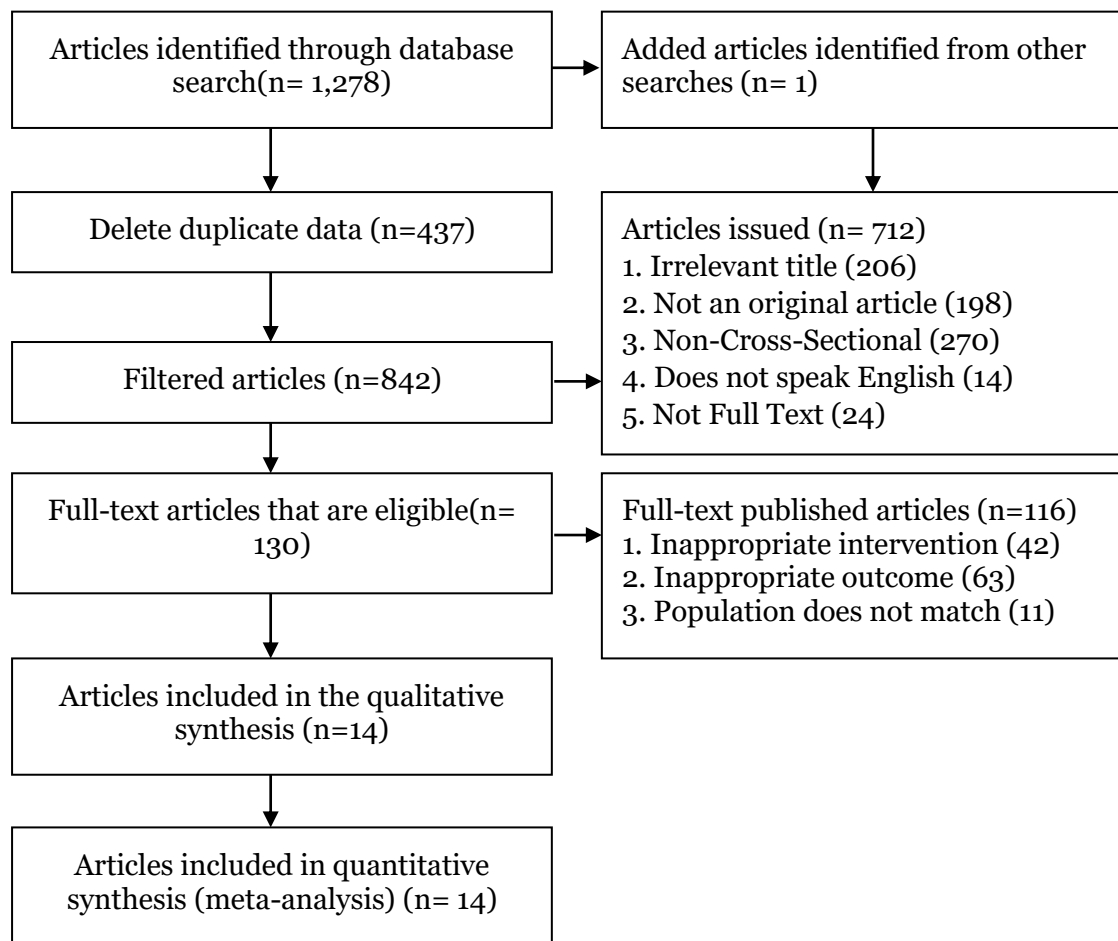| Articles included in quantitative synthesis (meta-analysis) (n= 14) |

Figure 1. PRISMA flow diagram

Table 1. Assessment of Study Quality

Publication	Research objectives/ focus	Cross-sectional	Method	Selection Bias	Representive sample	Sample size	Response achieved	Research instrument	Significant statistics	95% CI	Confounding	Results can be applied	Total
Reavey et al. 2020	1	1	1	0	1	0	0	1	1	1	1	1	8
Castillo-Martínez et al. 2003	1	1	1	0	1	0	0	1	1	1	1	1	8
Zhou et al. 2020	1	1	1	0	1	0	0	1	1	1	1	1	8
Chen et al. 2020	1	1	1	0	1	0	0	1	1	1	1	1	8
Ganesan et al. 2019	1	1	1	0	1	0	0	1	1	1	1	1	8
seif et al. 2015	1	1	1	0	1	0	0	1	1	1	1	1	8
Wei et al. 2009	1	1	1	0	1	0	0	1	1	1	1	1	8
Chang et al. 2009	1	1	1	0	1	0	0	1	1	1	1	1	8
Lin et al. 2007	1	1	1	0	1	0	0	1	1	1	1	1	8
Yamamoto et al. 2009	1	1	1	0	1	0	0	1	1	1	1	1	8
Chang et al. 2009	1	1	1	0	1	0	0	1	1	1	1	1	8
Palm et al. 2014	1	1	1	0	1	0	0	1	1	1	1	1	8
Rafique et al. 2018	1	1	1	0	1	0	0	1	1	1	1	1	8
Yu et al. 2016	1	1	1	0	1	0	0	1	1	1	1	1	8

Note:
Yes = 1 No = 0

Table 2. Description of the primary study of the effect of obesity on menstrual cycle disorders included in the meta-analysis

Author (year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Reavey et al (2020)	The UK	Cross-sectional	358	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Castillo-Martínez et al. (2003)	Mexico	Cross-sectional	120	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Zhou Xinyu et al. (2020)	China	Cross-sectional	1423	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Chen Xueyu et al. (2020)	China	Cross-sectional	5,373	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Ganesan et al. (2019)	India	Cross-sectional	163	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Seif et al(2015)	English	Cross-sectional	11,791	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Wei Shuying et al. (2009)	Australia	Cross-sectional	726	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders
Chang Pei et al. (2009)	Taiwan	Cross-sectional	1,095	Women of reproductive age	Obesity	Not obese	Menstrual cycle disorders

Table 3. Description of the primary study of the effect of stress on menstrual cycle disorders included in the meta-analysis

Author (year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome
Lin Hsin et al. (2007)	Taiwan	Cross-sectional	746	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders
Yamamoto.K et al. (2009)	Japan	Cross-sectional	264	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders
Chang Pei et al. (2009)	Taiwan	Cross-sectional	1095	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders
Palm Simona et al. (2014)	Switzerland	Cross-sectional	696	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders
Rafique N et al. (2018)	Arab	Cross-sectional	738	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders
Yu Mi et al(2016)	Korea	Cross-sectional	808	Women of reproductive age	Stressed	Unstressed	Menstrual cycle disorders

1. The effect of obesity on menstrual cycle disorders

Research related to the effect of obesity on menstrual cycle disorders comes from the continents of Asia, Europe and Australia, consisting of various countries including the UK, China, Taiwan, India and Australia. The description of each study can be seen in Table 2.
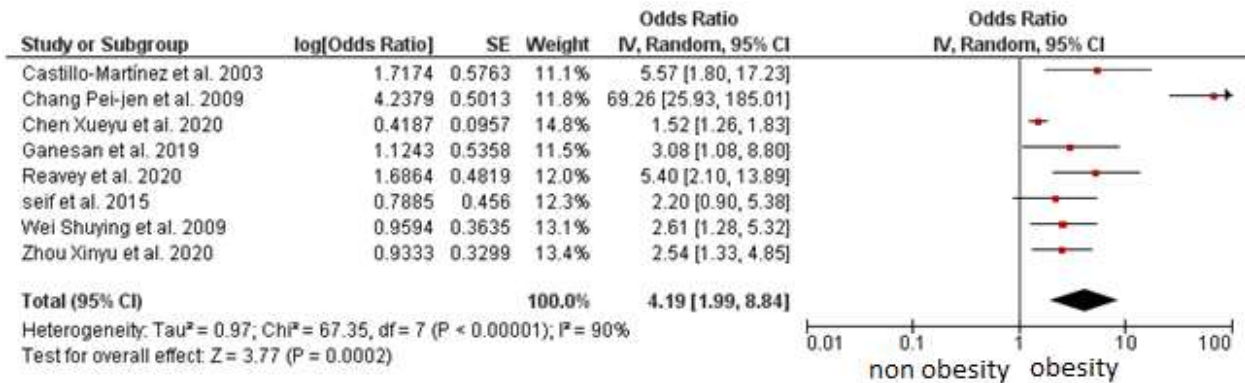
a. Forest Plot

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Castillo-Martínez et al. 2003	1.7174	0.5763	11.1%	5.57 [1.80, 17.23]
Chang Pei-jen et al. 2009	4.2379	0.5013	11.8%	69.26 [25.93, 185.01]
Chen Xueyu et al. 2020	0.4187	0.0957	14.8%	1.52 [1.26, 1.83]
Ganesan et al. 2019	1.1243	0.5358	11.5%	3.08 [1.08, 8.80]
Reavey et al. 2020	1.6864	0.4819	12.0%	5.40 [2.10, 13.89]
seif et al. 2015	0.7885	0.456	12.3%	2.20 [0.90, 5.38]
Wei Shuying et al. 2009	0.9594	0.3635	13.1%	2.61 [1.28, 5.32]
Zhou Xinyu et al. 2020	0.9333	0.3299	13.4%	2.54 [1.33, 4.85]
Total (95% CI)			100.0%	4.19 [1.99, 8.84]

Heterogeneity: Tau² = 0.97; Chi² = 67.35, df = 7 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.77 (P = 0.0002)

Figure 2. Forest plot meta-analysis effect of obesity and menstrual cycle disorders

The forest plot provides a summary of the data entered and gives weights for each study, effect sizes, methods and models used to perform the meta-analysis, confidence intervals used, impact estimates from each study, overall effect estimates, and statistical significance of the analysis. Interpretation of the results of the meta-analysis process can be seen through the forest plot. Figure 2 shows that there is an effect of obesity on the risk of experiencing menstrual cycle disorders. Obese women have a risk of experiencing menstrual cycle disorders 4 times compared to normal weight (aOR= 4.19; 95% CI = 1.99 to 8.84; p= 0.002). The heterogeneity of the study data shows I^2 = 90% so that the distribution of the data is declared heterogeneous (random effect model).
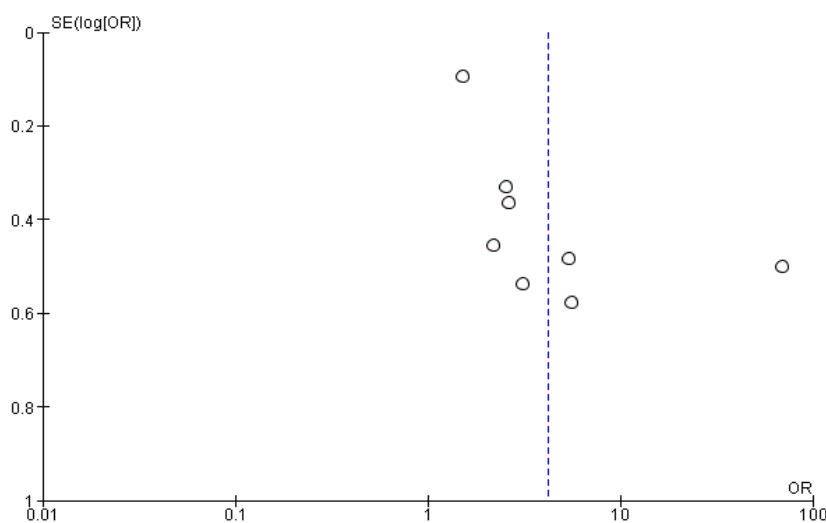
b. Funnel Plot

Figure 3. Funnel plot meta-analysis of the influence of obesity against cycle disturbance

A funnel plot is a plot that depicts the approximate size of the effect of each study on the estimate of its accuracy which is usually the standard error.

Figure 3 shows that there is an asymmetrical picture in the funnel plot which indicates there is a slight publication bias in the primary study with a small sample size, which overestimates the true effect, as evidenced by there are 3 plots on the right, 4 plots on the left.

2. The relationship between stress and menstrual cycle disorders

Research related to the effect of stress on menstrual cycle disorders comes from the continents of Asia and Europe, consisting of Taiwan, Switzerland, Arabia, Japan and Korea. An overview of each study can be seen in Table 3.

a. ForestPlot

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Chang Pei et al. 2009	0.5365	0.185	9.0%	1.71 [1.19, 2.46]
Lin Hsin et al. 2007	1.5686	0.1912	8.6%	4.80 [3.30, 6.98]
Palm Simona et al. 2014	0.0488	0.0148	36.1%	1.05 [1.02, 1.08]
Rafique N et al. 2018	0.2624	0.3158	3.7%	1.30 [0.70, 2.41]
Yamamoto.K et al. 2009	0.0296	0.01	36.5%	1.03 [1.01, 1.05]
Yu Mi et al. 2016	0.4511	0.2353	6.1%	1.57 [0.99, 2.49]
Total (95% CI)			**100.0%**	**1.28 [1.13, 1.45]**

Heterogeneity: Tau² = 0.01; Chi² = 76.10, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.89 (P = 0.0001)

Figure 4. Forest plot meta-analysis effect of stress and menstrual cycle disorders

The interpretation of the results of the meta-analysis of the relationship between obesity and the incidence of PCOS in women of childbearing age can be seen through the forest plot. Figure 4 shows that there is an effect of stress on the risk of experiencing menstrual cycle disorders. Women with stress had a risk of experiencing menstrual cycle disorders 1.28 times compared to women who did not experience stress (aOR = 1.28; 95% CI = 1.13 to 1.45; p = 0.001). The heterogeneity of the research data shows I2 = 93% so that the distribution of the data is declared heterogeneous (random effect model).
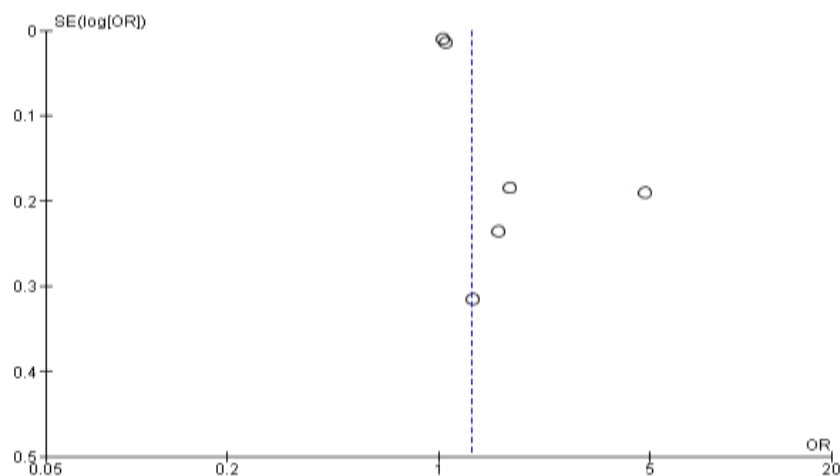
b. Funnel Plot

Figure 5. Funnel plot meta-analysis of the relationship between stress and menstrual cycle disorders

Based on Figure 5 funnel plot of the effect of stress on menstrual cycle disorders, there is an asymmetrical picture in the funnel plot which indicates there is a slight publication bias in the primary study with a small sample size, which overestimates the effect.

DISCUSSION

This systematic review and meta-analysis research is about the effect of obesity and stress on menstrual cycle disorders. The independent variable in this study was obesity and the dependent variable analyzed was menstrual cycle disorders.

This meta-analysis study uses research that controls confounding factors because the research involved is a study that uses multivariate analysis and the statistical results reported are adjusted odds ratio (aOR). The combined estimate of the relationship between obesity and stress on menstrual cycle disorders was processed using the RevMan 5.3 application. The results of the systematic study and meta-analysis are presented in the form of forest plots and funnel plots.

1. The effect of obesity on menstrual cycle disorders

There are 8 research articles from various countries using observational methods that can be used as sources for this meta-analysis research. The results of the forest plot show that there is an effect of obesity on the risk of experiencing menstrual cycle disorders. Obese women had a risk of experiencing menstrual cycle disorders 4 times compared to normal weight (aOR= 4.19; 95% CI= 1.99 to 8.84; p= 0.002).

This is in line with Reavey et al, (2020) which found that women with obesity had an increased risk of menstrual cycle lengthening 5.4 times compared to women with normal weight. Increased BMI will have an impact on endometrial func-

tion, increasing estrogen levels as a result of peripheral conversion of androgens by the adipose tissue aromatase enzyme.

Ganesan et al (2019) also conducted a similar study with the results that obese women had a 3.08 times risk of experiencing irregular menstrual patterns compared to women with normal weight. This study found a very strong and significant relationship between BMI and irregular menstrual patterns similar to various studies around the world. If the BMI is kept within the normal range or even switched to a lower weight category by adapting simple but proven effective measures like physical activity, dietary changes, etc., we can regulate the menstrual cycle to some extent without needing any medication.

A high percentage of body fat can cause an increase in androgens which play a role in producing estrogen with the help of the aromatase enzyme which converts androgens into estrogen in granulosa cells and fat tissue, so that with increasing body fat, estrogen increases which can cause hormonal imbalances and vice versa, the percentage of body fat Low levels cause a decrease in the production of the hormone estrogen so that it disrupts the balance and causes menstrual cycle disorders (Septian, 2017).

2. The effect of stress on menstrual cycle disorders

There are 6 cross-sectional research articles as a source of meta-analysis related to the effect of stress on menstrual cycle disorders. The results of the forest plot of research articles with this cross-sectional study showed that women with stress had 1.28 times the risk compared to women who were not stressed and the results were statistically significant (aOR= 1.28; 95% CI= 1.13 to 1, 45; p = 0.001).

The results of this study are supported by Chan Pei et al (2009) which states that

women with stress are 1.7 times more likely to experience menstrual cycle disorders compared to women who are not stressed. Psychological stress includes stressors in life, psychological stress or work stress resulting in longer cycles, cycle variability and pain during menstruation; However, women with excessive work pressure have also been shown to have shorter cycles. One of the mechanisms linking stress to menstrual function occurs through impaired function of the hypothalamic-pituitary-adrenal axis of the body's stress response so that glucocorticoids have a reciprocal interaction with ovarian hormones that will affect a woman's menstrual cycle.

Lin Hsin et al. (2007) also conducted a similar study on nurses in 4 public hospitals in Taiwan. Nurses' menstrual cycle was considered abnormal if it was less than 24 days or longer than 35 days. Demographic variables for logistic regression analysis included: self-perceived work stress level, age, body mass index (BMI), marital status, pregnancy history. However, not having a partner, having never been pregnant and working for less than 5 years were statistically associated with longer and irregular menstrual cycles. In addition, nurses who worked more than 40 hours per week were more at risk of experiencing irregular menstrual cycles (OR= 1.5, 95% CI= 1.1 to 2.1, p = 0.029). After adjusting for work stress, age, BMI, marital status, pregnancy history, occupation and working hours, only those with high levels of job stress had a statistically significant risk of irregular menstrual cycles (AOR= 4.8; 95% CI= 3.3 to 7.2, p<0.001). Work stress can disrupt endocrine function and biological rhythms that can cause irregular menstrual cycles, changes in abnormal menstrual bleeding patterns.

A study by Yamamoto et al. (2009) involved 264 students in Japan. Lifestyle factors such as smoking, alcohol consumption, exercise, dietary habits, physical factors such as body mass index (BMI), and menstrual factors such as age at menarche and menstrual duration are associated with premenstrual symptoms, menstrual pain, and irregular menstrual cycles. Menstrual cycle was defined as the period between the first day of menstrual flow and the day immediately before the next menstrual flow. Stress scores and BMI were shown to be significant predictors of experiencing irregular menstrual cycles. Students who had higher stress scores were more likely to experience irregular menstrual cycles. Students with high stress scores have a risk of 1.03 times experiencing irregular menstrual cycles compared to students with low stress scores.

In women who experience stress will occur conditions that disrupt homeostasis. Reproductive status is a reflection of a person's psychological state, if there is an increase in exposure to stress, reproductive function will automatically decrease to maintain body homeostasis. The stress system is regulated by the hypothalamic pituitary adrenal (HPA) axis and the autonomic system. The main mediators of the stress system include Cortocoptopin Relaxing Hormone (CRH), glicorcorticoids, and beta endorphins. CRH has various tissues such as ovaries, endometrium, hypothalamus and inflammatory tissue. Increased production of CRH and cortisol causes the restriction of GnRH secretion to decrease ovulation. This decrease in ovulation will affect the length of the proliferation and secretion period so that it affects the menstrual cycle (Rakhmawati, 2012).

AUTHOR CONTRIBUTION

Lutfi Annarahayu is the main researcher who chooses the topic, conducts a search for data collection in this study. Yulia Lanti

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