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Effectiveness of Hormone Based Therapies (Spironolactone and Combined Oral Contraceptives in the Management of Acne Vulgaris in Women: A Systematic review and meta-analysis

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ABSTRACT

Background: Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous follicular unit that often occurs. Acne is a skin disorder that is not life-threatening but is mostly complained of because it is aesthetically disruptive, which can cause significant psychological problems for sufferers. The management of acne vulgaris in female patients has its challenges. There are many histories of failed therapy using conventional therapy, such as with antibiotics or isotretinoin, and female patients have a predisposition to the condition of androgen excess. Also, the increasing awareness about limiting the use of antibiotics to prevent resistance in dermatological cases, including acne vulgaris, encourages other treatment options in the female patient population, one of which is hormone-based therapy. A systematic review and meta-analysis were performed of randomized clinical trials assessing the effects of Hormone Based Therapies (Spironolactone and Combined Oral Contraceptives) in the management of Acne Vulgaris in Women. **Methods**: Medline Pubmed, Scopus, Cochrane Library, the reference list, conference proceedings, researchers in the field of eligible studies were searched. Ten studies (n=1906 sub-jects) were included in qualitative analysis, of which eight studies (n=1842 subjects) were included in the meta-analysis. The age of the participant was greater than 14 years old. Intervention using combined oral contraceptives (n=8) or oral spironolactone (n=2). Duration of intervention (minimum six months for COC and three months for SL) and outcomes of mean difference number of acne vulgaris lesions before and after treatment. **Results:** Pooling of data using random-effects model found a significant difference in the mean difference in the number of lesions after treatment in the group receiving hormone-based therapy (spironolactone and combined oral contraceptives) and those receiving control therapy (p = 0.005). The overall mean difference was -0.890 ± 0.316. A negative value indicating the number of lesions after hormone-based therapy (spironolactone and combined oral contraceptives) was significantly lower than those receiving control thera-py (p = 0.005). **Conclusion:** From the results of the systematic review and meta-analysis conducted, it can be concluded that in the group given hormone-based therapy (spironolactone and Combined Oral Contraceptives), there was a decrease in the total number of acne vulgaris lesions compared to before treatment, and the mean difference in the number of lesions was significantly lower after getting hormone-based therapy (spironolactone and combined oral contraceptives) compared with controls.

Keywords: hormone-based therapy, spironolactone, Combined Oral Contraceptives, Acne Vulgaris

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Introduction

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous follicular unit that often occurs. This disorders is characterized by the presence of open comedo, closed comedo, papules, pustules or nodules with varying degrees and severity. The prevalence of acne is estimated to be 85% at 12-25 years of age. Acne is also considered as the third most crucial disease under the global burden of disease.[1,2] In Indonesia, around 15 million people suffer from acne vulgaris. This disease ranks in the top three of the number of visitors to Dermatoveneorology clinic in hospital and in esthetic clinic. In the Dermatoveneorology clinic of Dr. Kariadi Hospital Semarang, during 2008-2013, AV was the most common skin disease, as much as 15.3%.[3]

Acne vulgaris is a disease with a multifactorial cause. Four main factors play an essential role in acne's pathogenesis: increased sebum production, epidermal follicular hyperproliferation, the release of inflammatory mediators in the skin, and *Propionibacterium acnes* colonization. Other factors contributing to acne formation can be genetic, environmental, stress, emotions, medications, diet/food intake, or hormonal factors.[4]

Various acne therapies are available with different mechanisms of action. However, the management of acne vulgaris in female patients has its challenges. Many histories of failed therapy (not giving a good response) using conventional therapy, such as antibiotics or isotretinoin, and female patients have a predisposition to androgen excess conditions. Also, the increasing awareness about limiting the use of antibiotics to prevent resistance in dermatological cases, including acne vulgaris, encourages other treatment options in the female patient population, one of which is hormone-based therapy.[5,6]

Hormone-based therapy can be effective in acne because it can reduce circulating androgen levels and local androgen hormone levels and counteract these hormones' effects on the sebaceous glands and follicular keratinocytes.[7] The type of hormone-based therapy often used in the management of women's acne vulgaris is spironolactone and Combined Oral Contraceptives (COC). Spironolactone is a synthetic steroid androgen receptor blocker that will compete with testosterone and dihydrotestosterone (DHT) to bind to androgen receptors, thereby reducing sebum production triggered by androgens.[8] Whereas COC is a combination of oral progestins and estrogens that works by suppressing luteinizing production hormone by the pituitary gland, which then reduces androgen synthesis by the ovaries.[9]

There have never been systematic reviews and meta-analyses assessing Hormone Based Therapies' effects (Spironolactone and Combined Oral Contraceptives) in Acne Vulgaris's management in Women. Therefore, we conducted a systematic review and meta-analysis evaluating the efficacy of Hormone Based Therapies (Spironolactone and Combined Oral Contraceptives) in the management of Acne Vulgaris in Women.

Material and Methods

Literature Search

The following databases were searched until data analysis: Medline Pubmed, Scopus, Cochrane Library. The reference list, conference proceedings, researchers in the field of eligible studies were searched to identify additional studies.

The following Mesh terms were used for searching: "*contraceptives oral hormonal*" OR "*spironolactone*" AND "*acne vulgaris."* The literature search was performed by three reviewers independently using PRISMA flow diagram 2009.[10] Differences in opinion were resolved between all reviewers to reach consensus.

Inclusion criteria were: clinical trials with/without randomization, participants all woman, age range 14-50 years old, intervention: using hormone-based therapy in the form of

spironolactone or combined oral contraceptives in female acne vulgaris patients, the participant did not have any endocrine disorders, outcomes: mean difference number of acne vulgaris lesions before and after treatment.

Studies were excluded if they: were written neither in Indonesian nor English, were case report, serial case, letter, literature review.

Study Selection

Three reviewers conducted the study selection independently. Duplicate articles were removed. Title and abstract review, full-text review were assessed for eligibility using the predefined inclusion and exclusion criteria. Differences in opinion were resolved between all reviewers to reach a consensus.

Data extraction

Data extraction was performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only.[11] Differences in opinion during data extraction were resolved between all reviewers, and the consensus was reached.

Assessment of risk of bias

Risk-of-bias assessments were performed independently by three reviewers using The Cochrane Collaboration data collection form for RCTs only[11] and The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[12]

Data synthesis

Meta-analysis difference in weighted mean was conducted using Comprehensive Meta-Analysis A Computer Program for meta-analysis Version 3.3. Where data was not available to enable pooling, a descriptive synthesis was performed.

Results

Initial database searches identified 282 non-duplicate records. Ninety-nine were excluded during the title/abstract review, 27 were excluded during the full-text review. Ten studies were included in this review, of which eight studies were included for meta-analysis. Figure 1 gives details of the study selection process.

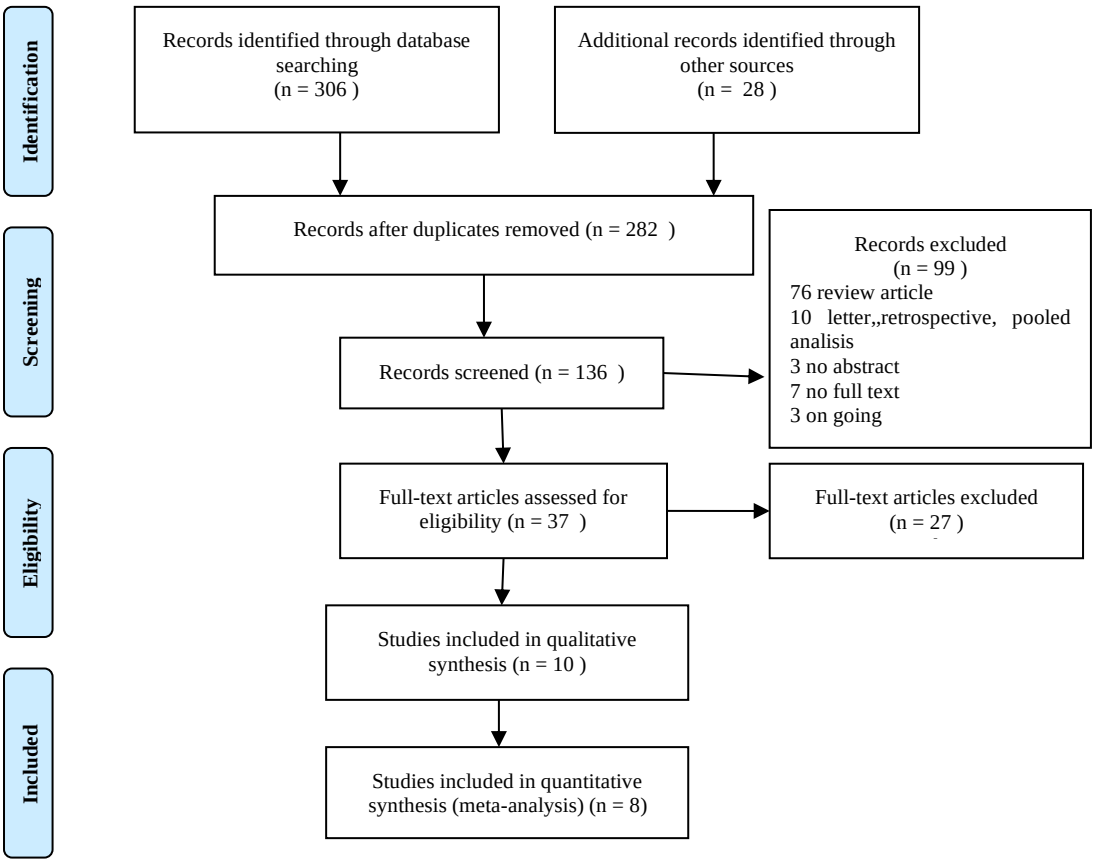

Figure 1. PRISMA flow diagram

Study Characteristics

The characteristics of included studies are given in Table 1. Study locations were conducted in the United States as much as 50% (n = 5), Thailand 20% (n = 2), England 10% (n = 1), Turkey 10% (n = 1) and Belgium 10% (n = 1) in the period 1986-2014. Sample age> 14 years. The total sample of 10 studies was 1906.

Table 1. Characteristics of included studies

Study	Age range (years)	N recruited/analyzed	Intervention group	Comparison group	Duration of intervention (month)
Jaisamrarn 2018[13]	18-45	200/180	EE 30 mcg/ CMA 2 mg	EE 30 mcg/ DRSP 3 mg	6
Jaisamrarn 2014[14]	18-45	201/188	EE 0,035 mg/NGM trifasik (H1-7:0,18 mg;H8-14:0,215 mg;H 15-21:0,25 mg;H22-28: tablet inaktif)	EE/DSG bifasik (H 1-7 : 0,04mg/0,025mg ; H 8-22: 0,03 mg/0,125mg ; H 23-28: stop)	6
Rosen 2003[15]	18-46	34/34	EE 0,3 mg/ DSG 0,15 mg	EE 0,3 mg/ LNG 0,15 mg	9
Thiboutot 2001[16]	>14	350/201	EE 20 mcg/ LNG 100 mcg	placebo	6
Vartiainen 2009[17]	16-35	172/136	EE/DSG kombifasik (H1-7: 40mcg/ 25 mcg; H 8-21: 30 mcg/ 125 mcg)	EE 35 mcg/CPA 2 mg	6
Lucky 1997[18]	15-49	257/160	EE 0,035 mg/NGM trifasik (H 1-7: 0,180; H8-14: 0,215; H19-21: 0,250 mg)	placebo	6
Leyden 2002[19]	> 14	371/371	EE 20 mcg/ LNG 100 mcg	placebo	6
Redmond 1997[20]	15-49	257/164	EE 0,035 mg/ NGM trifasik (H1-7: 0,18 mg; H8-14: 0,215 mg; H15-21: 0,25 mg; H22-28: tablet inaktif)	placebo	6
Muhlemann 1986[21]	20-35	29/21	SL 200 mg	placebo	7
Yemisci 2005[22]	18-31	35/35	SL 100 mg	tidak ada	3

1. Studies using Ethinyl Estradiol 0.035 mg / Norgestimat triphasic were included in 3 studies.

The first study (a) by Jaisamrarn et al. in 2014 was conducted on 201 study subjects with the treatment group (n = 93) receiving 0.035 mg / Norgestimat triphasic Ethinyl Estradiol therapy. The comparison group (n = 95) was given Ethinyl estradiol 0.04 mg / biphasic Desogestrel. Therapy is given orally, with a frequency of once a day in the morning. The study was conducted for six cycles. The results decreased the mean total number of lesions from the baseline compared to the sixth cycle. In the EE / NGM group, the mean change ± SD the total number of lesions was -13.4 ± 9.7; whereas in the EE / DSG group, the mean change ± SD the total number of lesions was -11.9 ± 10.1. The authors concluded that both preparations demonstrated comparable clinical effectiveness in their use to treat mild and moderate acne vulgaris.

The second study (b) by Lucky et al. in 1997 was conducted on 257 study subjects with the treatment group (n = 79). The comparison group (n = 81) was given a placebo. The results were

a decrease in the mean total number of lesions from the baseline compared to the sixth cycle, in the EE / NGM group mean baseline: 19.4; mean cycle 6: 7,7 and mean change ± SD the total number of lesions was -11.8 ± 8.9; whereas in the placebo group the mean baseline: 20.0; mean sixth cycle: 12.4; the mean change ± SD total number of lesions was -7.6 ± 8.9; and the p-value for the difference in the mean change of the two groups is 0.0001. The authors conclude that KOK containing EE / NGM is effective in treating moderate-grade acne vulgaris in women.

The third study (c) by Redmond et al. in 1997 was conducted on 257 study subjects with the treatment group (n = 84). The comparison group (n = 80) was given a placebo. The results showed a decrease in the mean total number of lesions from the baseline compared to the sixth cycle. In the EE / NGM group, the mean baseline: 53.9; mean cycle 6: 26.1 and mean change ± SD the total number of lesions was -27.8 ± 24.2; whereas in the placebo group, the mean baseline: 54.5; mean sixth cycle: 35.4; the mean change ± SD the total number of lesions was -19.1 ± 21.1; and the p-value for the difference in the mean change of the two groups is 0.001.

2. Studies using Ethinyl Estradiol 20 mcg / Levonorgestrel 100 mcg were included in 2 studies.

The first study (a) by Thiboutot et al. in 2001 was conducted on 350 study subjects with the treatment group (n = 93). The comparison group (n = 95) was given a placebo. The results decreased the mean total number of lesions from the baseline compared to the sixth cycle. In the EE / LNG group, the mean baseline: 58.72 ± 33.29; mean cycle 6: 33.85 ± 27.44 and mean change ± SD the total number of lesions was -25.15 ± 30.17; whereas in the placebo group, the mean baseline: 57.75 ± 33.93; mean sixth cycle: 41.62 ± 29.36; the mean change ± SD the total number of lesions was -16.13 ± 31.82; and the p-value for the difference in the mean change of the two groups is 0.007.

The second study (b) by Leyden et al. in 2002 was conducted on 371 study subjects with the treatment group (n = 185). The comparison group (n = 186) was given a placebo. The results decreased the mean total number of lesions from the baseline compared to the sixth cycle. In the EE / LNG group, the mean baseline: 71.98 ± 56.02; mean cycle 6: 57.26 ± 73.44 and mean change ± SD the total number of lesions was -14.72 ± 51.90; whereas in the placebo group, the mean baseline: 68.67 ± 46.90; mean sixth cycle: 65.19 ± 72.35; the mean change ± SD the total number of lesions was -3.48 ± 46.98; and the p-value for the difference in the mean change of the two groups is 0.0170.

3. A study using Ethinyl Estradiol / Desogestrel was included in 2 studies with different doses.

The first study (a) by Rosen et al. in 2003 was conducted on 34 study subjects with the treatment group (n = 17) receiving 0.3 mg / Desogestrel 0.15 mg Ethinyl estradiol therapy. The comparison group (n = 17) was given Etinil Estradiol 0.3 mg / Levonorgestrel 0.15 mg. The results decreased the mean total number of lesions from the baseline compared to the sixth cycle. In the EE / DSG group, the mean baseline: 28.2 ± 7.1; mean sixth cycle: 11.3 ± 3.3; mean reduction in the number of lesions 58.5% with p-value: 0.02; whereas in the EE / LNG group, the baseline means: 28.9 ± 7.4; mean sixth cycle: 17.6 ± 7.6; mean reduction in a number of lesions was 52.8% with p-value: 0.002.

The second study (b) by Vartiainen et al. in 2009 was conducted on 172 study subjects with the treatment group (n = 68) receiving combifasic Ethinyl Estradiol / Desogestrel therapy. the comparison group (n = 68) was given Ethinyl Estradiol 35 mcg / Cyproterone acetate 2 mg. The results decreased the mean number of lesions from the baseline compared to the sixth cycle. In the EE / DSG group, the mean baseline number of comedonal lesions: 11.3 ± 14.5; mean number of comedonal lesions cycle 6: 5.7 ± 10.8 mean number of baseline papule lesions: 17.1 ± 14.5; mean number of papule lesions cycle 6: 6.0 ± 7.9; mean baseline number of pustular

lesions: 3.8 ± 5.9; mean number of pustular lesions cycle 6: 1.2 ± 4.5; mean baseline number of nodule lesions: 0.6 ± 1.7; mean number of sixth cycle nodule lesions: 0.1 ± 0.3. Whereas in the EE / CPA group, the mean baseline number of comedonal lesions: 10.2 ± 14.0; mean number of comedonal lesions cycle 6: 2.8 ± 5.2 mean number of baseline papule lesions: 14.0 ± 11.7; mean number of papule lesions cycle 6: 4.2 ± 4.8; mean baseline number of pustular lesions: 3.2 ± 6.0; mean number of pustular lesions cycle 6: 0.4 ± 1.8; mean baseline number of nodule lesions: 1.4 ± 5.0; mean number of sixth cycle nodule lesions: 0.1 ± 0.7. The study results indicated that the overall reduction in lesions was statistically significant ($p \leq 0.003$), except for the reduction in the number of nodular lesions at the end of six months in the EE / DSG group.

4.Studies using Ethinyl Estradiol 30 mcg / Chlormadion acetate 2 mg were included in 1 study.

The study by Jaisamrarn et al. in 2018 was conducted on 200 research subjects with the treatment group (n = 90). The comparison group (n = 90) was given Ethinyl Estradiol 30 mcg / Drospirenone 3 mg. The results were a decrease in the mean total number of lesions from the baseline compared to the 6th cycle, in the EE / CMA group, the mean decrease in the number of lesions after the 6th cycle was -46.78 ± 2.11; whereas in the EE / DRSP group the mean reduction in the number of lesions after the 6th cycle was -38.90 ± 2.11. The study results showed that the total number of acne vulgaris lesions decreased significantly more in the EE / CMA group than in the EE / DRSP group with a value of p = 0.009.

5. Study using spironolactone (SL) was included in 2 studies with different doses.

The first study (a) by Muhlemann et al. in 1986 was conducted on 21 study subjects. Subjects were divided into two groups; one group was given spironolactone 200 mg per day, the other group was given a placebo. After undergoing therapy for three months, then for one month, both groups were given a placebo, then continued for three months. The two groups exchanged treatments; the initially given SL group, then continued for three months, was given a placebo, and the other groups. The outcome presented was a decrease in the mean number of inflammatory lesions. In the group, given SL 200 mg, the mean number of lesions decreased from 37.8 ± 5.8 to 12.9 ± 3.3 with a p-value <0.001. Whereas in the placebo group, the mean number of lesions decreased by 23.5 ± 3.2 to 24.7 ± 3.9 with a p value> 0.1.

The second study (b) by Yemisci et al. in 2005 was conducted on 35 study subjects who were given 100 mg of spironolactone per day, 16 days each month for three months. In this study, there was only one treatment group without a control or comparison group. The results showed a decrease in the mean total number of lesions from baseline compared to the end of the third month, the mean before therapy: 32.86 ± 16.15; mean after three months of therapy: 6.92 ± 4.99 with p-value <0.01.

Risk of Bias in included studies

The research articles that included in the meta-analysis are eight studies, i.e., Jaisamrarn et al. 2014, Lucky et al. 1997, Redmond et al. 1967, Thiboutot et al. 2001, Leyden et al. 2002, Rosen et al. 2003, Vartiainen et al. 2009, and Jaisamrarn et al. 2018, who reported differences in the mean total number of acne vulgaris lesions before and after treatment.

The risk of bias of eight studies included in the meta-analysis was performed using The Cochrane Collaboration data collection form for RCTs only[11] and The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.[12]

A study by Rosen et al., Jaisamrarn et al. (1), Redmond et al., Thiboutot et al., Lucky et al., and Jaisamrarn et al. (2) as a whole is categorized as low risk of bias. Leyden et al. did not clearly state that "blinding" was carried out on the research output assessment so that it could not be assessed as to whether it was a low risk or high risk. In Vartiainen et al., an open RCT study,

the text states that the allocation of study subjects was carried out randomly, but the randomization method was not stated to assess the potential for bias. "Blinding" on the subject and the output rater was not performed, so there was a high risk of bias. Details of the assessment are given in Table 2.

Table 2. Risk of bias of included studies in the meta-analysis

	Random sequence generation	Allocation concealment	Blinding (participants and	Blinding (outcome assessment)	Selective reporting	Other sources of bias	Incomplete outcome data	Other bias	Overall
Rosen MP et al.	+	+	+	+	+	+	+	+	+
Jaisamrarn et al. (1)	+	+	+	+	+	+	+	+	+
Redmond et al.	+	+	+	+	+	+	+	+	+
Leyden et al.	+	+	+	?	+	+	+	+	+
Thiboutot et al.	+	+	+	+	+	+	+	+	+
Lucky et al.	+	+	+	+	+	+	+	+	+
Jaisamrarn et al. (2)	+	+	+	+	+	+	+	+	+
Vartiainen et al	?	?	-	-	+	+	+	+	-

Meta-analysis

The results of the meta-analysis showed that there was a significant difference between the mean difference in the number of lesions after the treatment group receiving hormone-based therapy (spironolactone and combined oral contraceptives) and those receiving control therapy (p = 0.005). The overall mean difference was - 0.890 ± 0.316. A negative value indicating the number of lesions after hormone-based therapy (spironolactone and combined oral contraceptives) was significantly lower than those receiving control therapy (p = 0,005, I^2=96,534, eight RCTs). (Figure 2)

Discussion

This is a systematic review and meta-analysis evaluating the efficacy of Hormone Based Therapies (Spironolactone and Combined Oral Contraceptives) in the management of Acne Vulgaris in Women. The management of acne vulgaris in female patients has its challenges. There are many failed therapy histories (not giving a good response) using conventional therapy, such as antibiotics or isotretinoin. Female patients have a predisposition to androgen excess conditions. In addition, the increasing awareness about limiting the use of antibiotics to prevent resistance in dermatological cases, including acne vulgaris, encourages the use of other treatment options in the female patient population, one of which is hormone-based therapy.[5,6]

Muhlemann et al. 1986 and Yamiscii et al. 2005 gave negative results on the mean difference in the number of lesions before and after therapy. It indicates a decrease in the mean number of lesions after administration of spironolactone therapy.

The analysis results are consistent. Spironolactone has an anti-androgenic effect by competing with testosterone and DHT to bind to androgen receptors, inhibiting androgen synthesis by reducing the 17B-HSD type 2 enzyme production inhibiting the 5α-reductase enzyme, and increasing levels of steroid hormone-binding globulin. (SHBG), to reduce circulating free testosterone. The reduced number and binding of androgens to the receptors results in decreased sebum production and keratinocyte proliferation, reducing acne vulgaris lesions.[12]

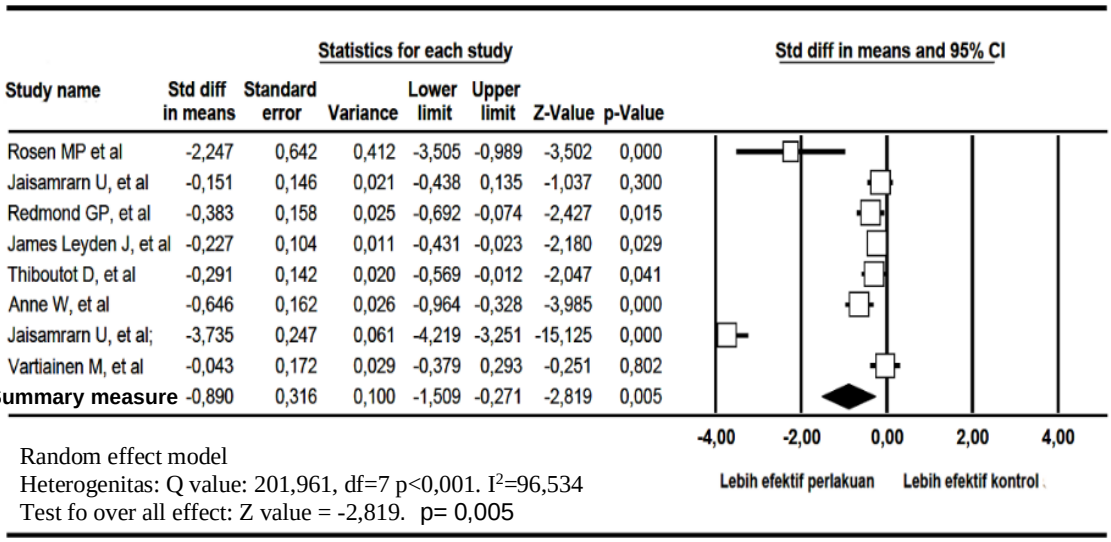

Figure 2. Results of meta-analysis on the effectiveness of hormone-based therapy (spironolactone and combined oral contraceptives) on the number of acne vulgaris lesions

The results of the analysis in the research of Rosen et al., Jaisamrarn et al. (1), (2), Redmond et al., Leyden et al., Thiboutot et al., Lucky et al., Vartiainen et al., which used Combined Oral Contraception also showed mean differences in the number of lesions. Before and after therapy, the value is negative. It indicates a decrease in the mean number of lesions after therapy administration.

The analysis results are appropriate that COC, which consists of progestins and estrogen, affects reducing androgen production through the suppression mechanism of luteinizing hormone production, increasing levels of sex hormone-binding globulin (SHBG), and inhibiting 5α-reductase. The reduced androgen production has the effect of decreasing sebum production and keratinocyte proliferation, thus reducing the number of acne vulgaris lesions.[23,]

Conclusion

From the results of the systematic review and meta-analysis carried out, it can be concluded that in the group given hormone-based therapy (spironolactone and Combined Oral Contraception), there was a decrease in the total number of acne vulgaris lesions compared to before treatment. The mean difference in the number of lesions was significantly lower after getting hormone-based therapy (spironolactone and combined oral contraceptives) compared with controls.

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Nil.

Conflict of Interest

There is no conflict of interest

Abbreviations :

COC: Combined Oral Contraceptives

RCT: Randomized Controlled Trial

SL: Spironolactone

Mesh: Medical subject headings

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

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