REVIEW ARTICLE

THE EFFECTIVENESS OF PRASTERONE VS PLACEBO THERAPY AS THE VULVOVAGINAL ATROPHY TREATMENT IN MENOPAUSAL WOMEN: META-ANALYSIS STUDY

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ABSTRACT

Background : Vulvovaginal atrophy is a condition that often occurs in menopausal women due to Estrogen decreased. Prasterone (DHEA) is a steroid hormone that can be converted into Estrogen in the target tissue. **Objective :** A Meta-analysis study was conducted to evaluate the effectiveness of administering Prasterone as Vulvovaginal Atrophy therapy in menopausal women, by evaluate the number of Superficial Cells, Parabasal Cells, vaginal pH, and Dyspareunia. **Methods :** A systematic data search was performed on a medical database (PUBMED, Google scholar, Cochrane). Inclusion criteria: (1) randomized study of Prasterone as Vulvovaginal Atrophy therapy in postmenopausal women, (2) all-inclusive papers can be accessed completely (from 583 articles found, we excluded 580 articles, the result is 3 RCT analyzed) and (3) the data obtained can be accurately analyzed. **Results:** Three RCTs with a total of 696 patients were analyzed. The average number of Superficial Cells (mean difference [MD] 7.63, and 95% [CI] 7.57 to 7.70 (P <0.00001). The average number of Parabasal Cells (mean difference [MD] -29.84, and 95% [CI] -30.25 to -29.44 (P <0.00001). The average number of vaginal pH (mean difference [MD] -0.69, and 95% [CI] -0.70 to -0.68 (P <0.00001). The average number of Dyspareunia (mean difference [MD] -0.38, and 95% [CI] -0.39 to -0.37 (P <0.00001). All diamonds do not intersect the vertical line, and have p <0.05, it proves that there are significant differences between the two groups. All non-hysterectomized women have an atrophic or inactive endometrium. Side effects that are often complained of are headache and application site discharge. **Conclusion** This meta-analysis concludes that Prasterone therapy has a significant therapeutic effect for Vulvovaginal Atrophy in menopausal women

INTRODUCTION

The layers of vaginal walls consist of 4 layers, namely Basal cells, Parabasal cells, Intermediate cells, and Superficial cells. In the women with normal estrogen levels, around 15%-30% of cells were Superficial cells and the remaining were Intermediate cells. If Parabasal cells were found, it might be due to the Estrogen deficiency that happened in the women. One of the factors of Estrogen deficiency was menopause.
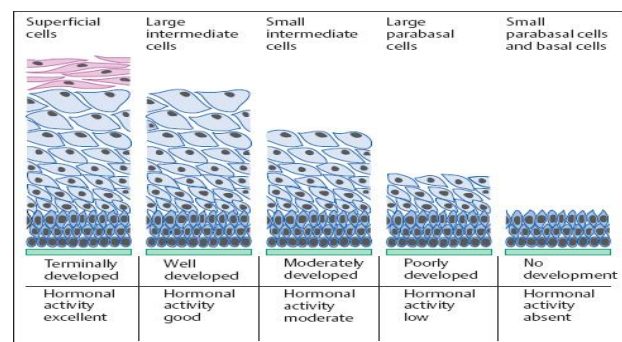
Figure 1. The Layers of Vaginal Walls

Vulvovaginal Atrophy (VVA) is a condition the frequently occurs in menopausal women. It is characterized by thinning of the vaginal epithelium, reduced vaginal lubrication, and increased fragility of the epithelium. The symptoms of VVA include the drying of the vagina, inflammation, burning sensation, and pain during sexual activities (Dyspareunia). The menopause-related hormone changes, especially lack of estrogen secretion, are the primary causes of VVA[1]. Before reaching menopause, the dominant cells are the superficial cells, and they only exist in some parabasal cells. Meanwhile, after menopause, the total parabasal cells increase followed by the absence of superficial cells [2].

The frequently used therapies for VVA treatment are non-hormonal therapy (lubricant) and hormonal therapy (topical estrogen), and the selective estrogen receptor modulators/SERMs (Ospemifene). The systemic estrogen is not given to avoid the potential stimulation effect of estrogen in the endometrium and breasts [3].

DHEA (Dehydroepiandrosterone) is a steroid hormone produced by the adrenal gland that is then changed into testosterone and estrogen. During menopause, DHEA becomes the main source of estrogen. However, the DHEA levels decrease as people get older and only 25% of menopausal women are estimated to have enough DHEA to avoid menopause symptoms, such as VVA[3]. DHEA replacement therapy is an effective approach that minimizes the potential risk related to estrogen-based therapy [3].

Prasterone is a synthetic DHEA that is biologically and biochemically identical to the endogenous human DHEA. In the peripheral target tissues, DHEA is altered into active intracellular estrogen and androgen by tissue-specific steroidogenic enzymes. Intravaginal prasterone (Intrarosa) has been used in Europe for VVA treatment in menopausal women[5]. Prasterone has been approved in the U.S. for Dyspareunia treatment due to menopause [6]. The dosage used is 6.5 mg of the vaginal suppository.

This paper was arranged to evaluate the effectiveness of prasterone vs placebo therapy as the VVA treatment in menopausal women using Meta-analysis method.

METHOD
Data Search Strategy

The search for literature systematically had been done using PUBMED, Google Scholar, and Cochrane Central Register of Controlled Trials to collect randomized studies (Randomized Controlled Trials/RCT) that investigated the use of Prasterone in menopausal women suffering from VVA. The researchers tried to find the database using the combination of some terms, such as "Prasterone, Placebo, VVA, menopause, and RCT".

Inclusion Criteria

Some of the following criteria had been used in the selection. (1) Randomized study

Table 1. The Quality Assessment of each Study. A: all qualities for criteria are fulfilled; ITT: intention-to-treat; ANCOVA: Analysis of Covariance; Pr: Prasterone; Pl: Placebo

| Study	Allocation sequence	Hidden Allocation	Therapy Group	Control Group	*Blinding*	Sample size calculation	Statistic Analysis	ITT Analysis	Level of study quality
Labrie (2011)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A
Archer (2015)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A
Labrie (2018)	A	A	Pr	Pl	A	yes	ANCOVA	Yes	A

(randomized controlled trials) on Prasterone as the Vulvovaginal Atrophy (VVA) treatment in menopausal women, (2) all inclusion papers can be accessed completely, and (3) the collected data can be analysed accurately.

Quality Assessment of the Study

We assessed the validity of each study independently by using the criteria mentioned in the Cochrane Handbook for Systematic Reviews of Interventions. We discussed the topic if there was a different point of view. Each study was put into some classifications and assessed based on the category of quality, namely, quality A if the study had low risk of bias; quality B if the study had moderate risk of bias, or quality C if the study had high risk of bias (Figure 2 and Figure 3).
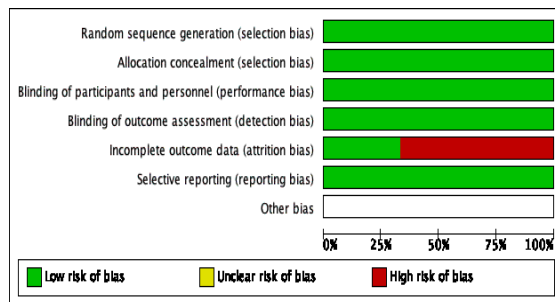
Figure 2. The Conclusion of the Stratification of the Risk of Bias in All Articles in This Meta-analysis
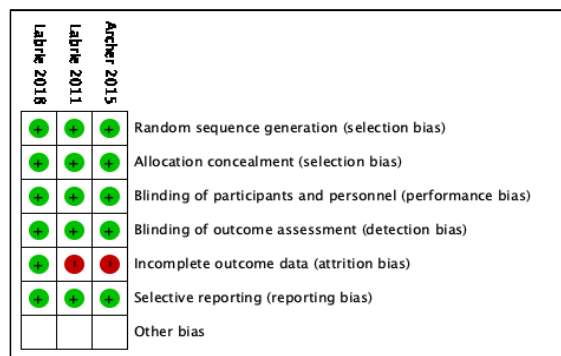
Figure 3. The Assessment of the Writer's Risk of Bias Against Each Inclusion Article

Data Extraction

The followings are the important information collected from each study: (1) main author; (2) the country of the research location; (3) total sample; (4) year of publication; (5) therapy in patients; (6) the data of the mean score of superficial cells; (7) the mean score of parabasal cells; (8) the mean score of vaginal pH; (9) and the mean score of Dyspareunia complaints.

Statistical Analysis and Meta-Analysis

The effect of therapy is expressed using the comparison of the outcome from the therapy group and the control group. In this paper, the outcome was reported as the continuous variables, whereby it had several possible results. The effect of the therapy was expressed as the 'mean score difference'. This score calculated by obtaining the mean scores in both the therapy group and the control group, and then the difference was calculated.

Meta-analysis was arranged using the Review Manager (RevMan) version 5.3. (Cochrane Collaboration, Oxford, UK). This paper assessed the mean difference of superficial cells, the mean difference of superficial cells, the mean difference of parabasal cells, the mean difference of vaginal pH, and the mean difference of Dyspareunia complaints.

The researchers used the fixed-effect and random-effect of meta-analysis for data combination, whereby it assumed logically that several studies had a similar therapy effect estimation.

RESULT
Characteristic of the Studies

Data search resulted in 583 articles. A total of 585 studies had been excluded based on the description in the abstract by seeing the inclusion and exclusion criteria that had been described before. After a series of the selection process, it collected 3 inclusion articles in total for meta-analysis (Figure 3). Table 1 shows additional information related to inclusion articles.

Individual Quality of the Study

All inclusion studies were random and double-blind, and all articles had been passed the randomization process. All inclusion RCTs performed the calculation of power in determining the optimum total sample (Table 1).

We had assessed explicitly whether the relevant studies had a high risk of bias based on the criteria mentioned in the Handbook[7]. Based on the assessment, we assessed the degrees of possibility and the direction of bias and the possibility of these points to influence the outcome of the study. We then analysed the sensitivity in exploring the effect of bias.
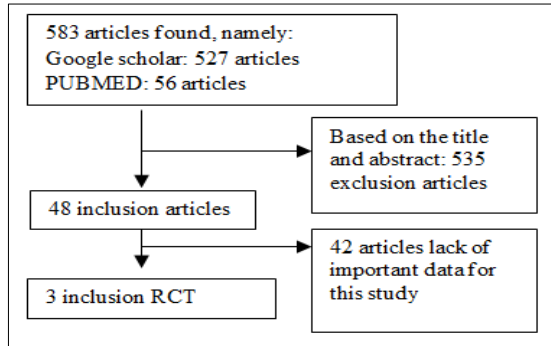
Figure 3. Path Diagram of the Process of Selecting Studies.

Effectiveness

The Mean Score of Superficial Cells

Three inclusion RCTs with the outcome of the mean score of superficial cells, from the cohort, contained 696 samples (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 4). The estimation of fixed-effects from the mean score difference was 7.63 and 95% CI was around 7.57 to 7.70 (P <0.0001). This analysis result showed that Prasterone had a more significant effect on increasing the mean score of superficial cells than that of Placebo.

The Mean Score of Parabasal Cells

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the Placebo group) (Figure 5). The estimation of fixed-effects from the mean

difference was -29.84 and 95% CI was around -30.25 to -29.44 (P <0.0001). The result of this analysis showed that Prasterone had a more significant effect on decreasing the mean score of parabasal cells than that of Placebo.

The Mean Score of Vaginal pH

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 6). The estimation of fixed-effects from the mean difference was -0.69 and 95% CI was around -0.70 to –0.68 (P <0.0001). The result of this analysis showed that Prasterone had a more significant effect on decreasing the mean score of vaginal pH than that of Placebo.

Dyspareunia Complaints

Three RCTs contained 696 samples in total (436 samples in the Prasterone group and 260 samples in the placebo group) (Figure 6). The estimation of fixed-effects from the mean difference was -0.38 and 95% CI was around -0.39 to –0,37 (P <0.0001). This analysis result showed that Prasterone had a more significant effect on decreasing the Diyspareunia complaints than that of Placebo.

From the four forest plots, the diamond was not tangential to the vertical line. Hence, it might be inferred that the was a difference in the result between the experimental group and the control group. The four analyses had a p-value of less than 0.05, proving that there was a significant difference between the two variables. The three studies above were heterogenous since not all of the Confidence Interval intersected the vertical line of the diamond.
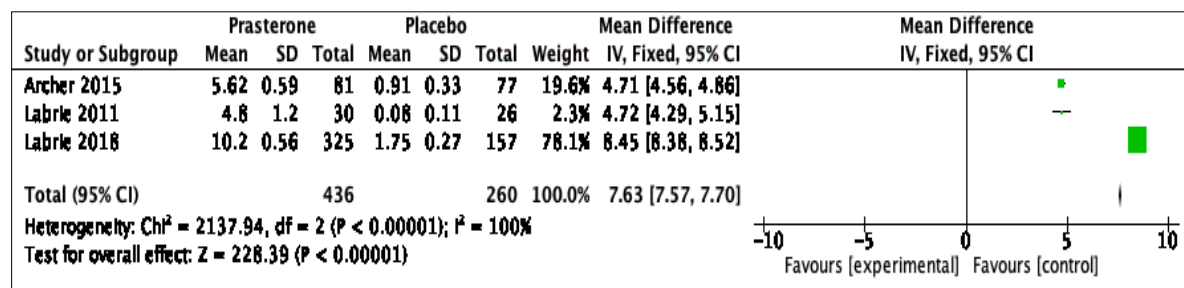
Figure 4. The Forest plot shows the mean difference in superficial cells. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.
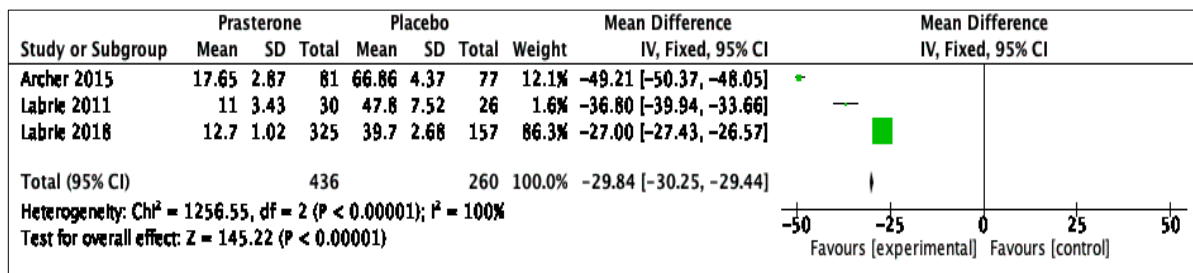
Figure 5. The Forest plot shows the mean difference in Parabasal cells. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.
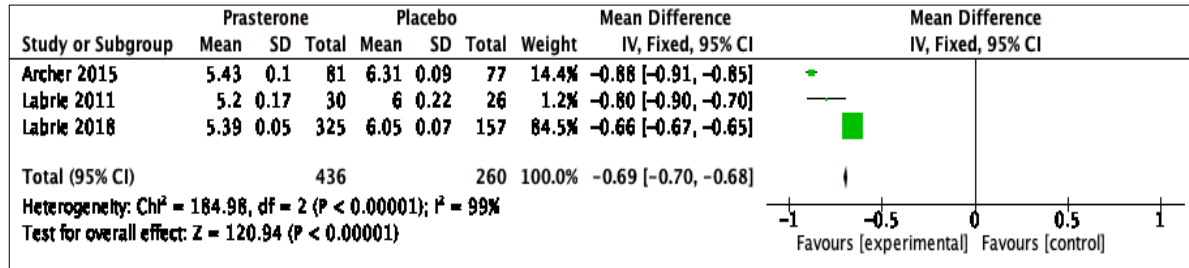

Figure 6. The Forest plot shows the mean difference in vaginal pH. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.
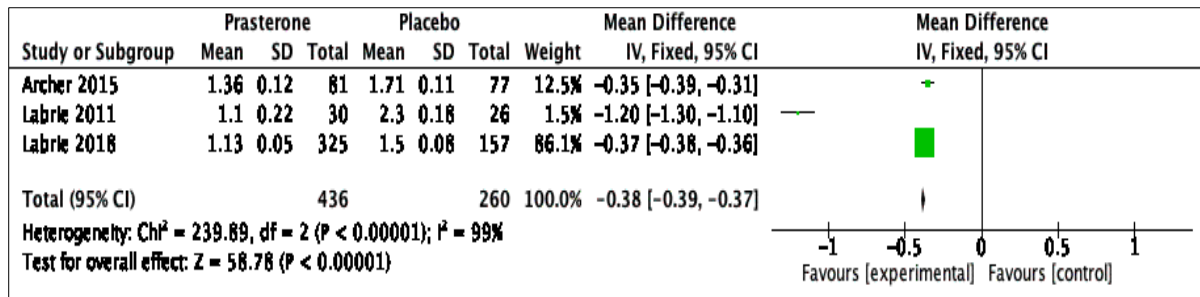

Figure 7. The Forest plot shows the mean difference in Dyspareunia complaints. SD, standard deviation: IV. inverse variance: CI. confidence interval: df. degrees of freedom.

DISCUSSION

Prasterone has been used in the U.S. and Europe since 2016 as the VVA treatment in menopausal women. The following is the pharmacologic treatment for VVA complaints.

The excellence of giving the Prasterone was that it did not cause significant changes in steroid hormone levels in the serum. The Estrogen and Testosterone levels were still at the normal range for menopausal women, and they were known [9].

From the result of the 2 RCTs that had been analyzed, besides the improvement of 4 investigated variables, Prasterone also had advantageous Androgen effects, such as the

decreased of the drying in the vagina, the decreased irritation/itchiness in the vagina, the decreased vaginal fluid, and the improved integrity of vaginal epithelium [9].

Drug	Available Strengths	Cost[b]
Oral		
Osphena (Shionogi)	60 mg ospemifene/tab	$556.60
Vaginal		
Rings		
Estring (Pfizer)	2 mg/ring (0.0075 mg estradiol/d)[c]	406.90
Femring (Allergan)	0.05, 0.1 mg estradiol/d[c]	422.50
Inserts		
Intrarosa (Endoceutics)	6.5 mg prasterone/insert	525.00
Vagifem (Novo Nordisk)[d]	0.01 mg estradiol/tab	765.70[e]
Creams		
Estrace (Allergan)	0.01% cream (0.1 mg estradiol/gram)	287.60[f]
Premarin Vaginal Cream (Pfizer)	0.625 mg conjugated estrogens/gram	345.40[g]

Figure 8. The Pharmacologic Treatment for VVA

The side effects that the RCT subjects complained about were white vaginal discharge/leucorrhoea, urinary tract infection (UTI), and headache. The endometrial conditions that had been evaluated in the 12th week mostly resulted in endometrial atrophy. No significant histological finding existed in all of the results of biopsy[9].

This Meta-analysis only included double-blind RCT. The quality of all studies in this meta-analysis was quite high based on the assessment criteria of Review Manager 5.3 program. However, the total inclusion study was not adequate in compiling the clinical recommendation against the patients. In addition, the long-term effect (effectiveness and side effects) could not be proven in this study. Consequently, the writers suggest a further investigation from big-scale studies in the patient population of this study.

CONCLUSION

This Meta-analysis concludes that Prasterone has significant therapeutic effects in patients experiencing Vulvovaginal Atrophy due to Menopause, and it has been proven safe to be consumed.

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