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Original Article

Comparison Between Combined Oral Contraceptive Pills and Selective Serotonin Reuptake Inhibitors in the Management of Moderate to Severe Premenstrual Syndrome

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Abstract *- Background: Premenstrual syndrome, in its moderate and severe stages, is a troubling condition for many women because of the disturbance it causes on the personal, professional, and social levels. Therefore, treating it correctly and appropriately has great importance in improving the psychological and physical condition of afflicted women, as well as increasing productivity and interaction with society. Objective: The main objective of the study is to compare the effectiveness of the two drug groups that are considered the main options in the management of clinically significant symptoms of premenstrual syndrome, which are combined oral contraceptives and selective serotonin reuptake inhibitors. Patients and Methods: This was a prospective, comparative cohort study that included a sample of 150 women who met the inclusion criteria for the study. The sample was divided into two groups, each group including 75 women, where the first group received treatment with selective serotonin reuptake inhibitors, and the second group received treatment with combined oral contraceptives; a comparison was conducted between the two drug groups in terms of their effect on the severity of the psychological and physical symptoms of premenstrual syndrome and also in terms of their side effects. Results: There was a remarkable improvement in both groups in terms of psychological and physical symptoms, as these symptoms ranged in severity before treatment from moderate to severe, and after treatment, symptoms ranged from non-existent in the vast majority of women to mild in the remaining percentage of women, with a slight superiority for selective serotonin reuptake inhibitors in the management of psychological symptoms. Conclusion: Both combined oral contraceptives and selective serotonin reuptake inhibitors can be used in the management of moderate to severe premenstrual syndrome, which causes functional disability in affected women, as both drug groups showed similar effectiveness in managing this syndrome.*

Keywords *- Premenstrual syndrome, Selective serotonin reuptake inhibitors, Combined oral contraceptives.*

1. Introduction

Premenstrual syndrome is a group of psychological and physical symptoms that occur periodically during the second half of the menstrual cycle, which is the luteal phase, and disappear with the onset of menstruation or within a few days of it. The symptoms of this syndrome range in severity from mild to severe, and in severe stages, it can impair a woman's daily life and affect her work and social relationships [1]. The most common physical symptoms of the syndrome include abdominal bloating - fatigue and weakness - breast pain - headache - dizziness - hot flashes. [2]. The most common psychological symptoms of the syndrome include mood swings - irritability - depressed mood - anxiety - appetite disturbances - loss of pleasure in usual activities [2]. A severe case of premenstrual syndrome is called “premenstrual dysphoric disorder” and is characterized by severe physical and psychological symptoms that impair the woman's professional and social life [1,3]. Most women in the period of reproductive activity suffer from one or more mild psychological or physical symptoms a day or two before the start of menstruation so that these symptoms do not impair the woman’s practical and professional life and thus do not express premenstrual syndrome [4]. Premenstrual syndrome is triggered by the cyclic changes of ovarian hormones during the luteal phase of the menstrual cycle in women who are predisposed, that is, those who are sensitive to these changes. Changes in ovarian hormones affect the work of central neurotransmitters, most notably serotonin, which is considered the neurotransmitter most implicated in the pathogenesis of premenstrual syndrome, as its decrease plays an important role in the occurrence of premenstrual syndrome [3]. Combined oral contraceptives and their effect on the

syndrome: These medications inhibit the hypothalamic-pituitary-ovarian axis and ovulation and thus prevent the effect of ovarian steroids on the function of neurotransmitters and thus the occurrence of premenstrual syndrome. The best and most effective of them, according to several studies, are those that contain drospirenone in their composition. Selective serotonin reuptake inhibitors and their effect on the syndrome: These medications raise the level of the neurotransmitter "serotonin" in the brain, as several studies have shown that the level of serotonin is low in women with premenstrual syndrome in the luteal phase of the menstrual cycle.

2. Patients and Methods

2.1. Study Population

The research sample consisted of 150 women who were diagnosed with premenstrual syndrome according to the criteria of the American Association of Obstetricians and Gynecologists (ACOG). The inclusion criteria: • Moderate to severe symptoms that cause impairment in a woman's social and professional life. Exclusion criteria: • Mild symptoms that do not cause functional impairment. • Any untreated disorder in the thyroid gland. The study sample of 150 women was divided into two groups, each group consisting of 75 women. We were careful to include married women who wanted to prevent pregnancy in one group. The women of the first group were placed on a treatment plan with a drug containing two substances, "Drospirenone 3 mg and ethinyl estradiol 20 mcg", starting from the first day of menstruation for 21 days for a period of three months, with symptoms and their severity recorded after treatment using a premenstrual syndrome screening tool. The women of the second group were placed on a treatment plan with "escitalopram" at a dose of 10 mg in the intermittent regimen, which is one pill daily, from the 15th day of the cycle for 10 days, for a period of three months, with the symptoms and their severity after treatment recorded using a premenstrual syndrome screening tool. Side effects were documented for both drug groups during the treatment period.

2.2. Ethical Consideration

All patients were provided with complete and clear informed consent after discussion about the study. This study was performed following the Declaration of Helsinki.

2.3. Statistical Analysis

Statistical analysis was performed by using the IBM SPSS version20. Basic Descriptive statistics included means, Standard Deviations (SD), median, Frequency and percentages. To examine the relationships and comparisons between the two groups, the chi-square test was used. Independent t student tests were used to compare 2 independent groups. Friedman test was used for differences between groups when the dependent variable being measured is ordinal. All the tests were considered significant at 5% types I error rate ($p<0.05$), β:20%, and power of the study:80%.

3. Results

3.1. Ages

About 45% of women in the study sample were in the age group of 30-35 years; about 39% of women were in the age group of 25-30 years, and about 15% were in the age group of 20-25 years (see Table 1).

Table 1. Distribution of research sample of 150 women according to age groups

Age Groups	Number	Percentage %
30-35	68	45.4%
25-30	59	39.3%
20-25	23	15.3%
The Sum	150	100%

The average age of women in the first group was 24.98±4.8, and in the second group was 26.11±3.9. There were no statistically significant differences between the two research groups with regard to the mean values for age ($p>0.05$) (see Table 2).

Table 2. Average values for age in both research groups

	Study Population		P-value
Age (year)	Selective serotonin reuptake inhibitors	Combined oral contraceptives	
	26.11±3.9	24.98±4.8	0.09

3.2. Symptoms Distribution

The distribution of psychological symptoms in the research sample from the most common to the least common was as follows: Mood swings: 87.3% - Irritability: 84% - Anxiety: 80.7% - depressed mood: 74.7% - Appetite changes: 74% - Poor concentration: 72.7% - Sleep disturbances: 63.3% (see Table 3)

Table 3. Distribution of psychological symptoms in a sample of 150 patients

Physiological Symptoms	number	Percentage%
Mood Swings	131	87.3%
Irritability	126	84%
Anxiety	121	80.7%
Depressed mood	112	74.7%
Appetite changes	111	74%
Poor concentration	109	72.7%
Sleep Disturbances	95	63.3%

Table 4. Distribution of physical symptoms in a sample of 150 patients

Physical symptoms	Number	Percentage
Abdominal bloating	129	86%
Breast tenderness	118	78.7%
Headache	76	50.7%
Weakness	74	49.3%
Skeletal pain	71	47.3%
Dizziness	47	31.3%
Hot flashes	44	29.3%

The distribution of physical symptoms in the research sample from the most common to the least common was as follows: Abdominal bloating: 86% - Breast tenderness: 78.7% - Headache: 50.7% - Weakness: 49.3% - Skeletal pain: 47.3% - Dizziness: 31.3% - Hot flashes: 29.3% (see Table 4)

3.3. Severity of Symptoms

The Psychological symptoms ranged in severity before treatment from moderate to severe in both groups. There were no statistically significant differences between the two groups regarding the distribution of psychological symptoms according to their severity before treatment ($p>0.05$) (see Table 5)

After treatment, the psychological symptoms completely disappeared in the vast majority of women in both groups and became mild in the remaining percentage of women, with no statistically significant differences between the two groups in terms of symptom distribution ($p>0.05$).

The improvement in psychological symptoms was slightly better in the serotonin reuptake inhibitor group (see Table 6 and Figures 1 and 2).

The Physical symptoms ranged in severity before treatment from moderate to severe in both groups. There were no statistically significant differences between the two groups regarding the distribution of physical symptoms according to their severity before treatment ($p>0.05$) (see Table 7)

After treatment, the physical symptoms completely disappeared in the vast majority of women in both research groups and became mild in the remaining percentage of women, with no statistically significant differences between the two groups in terms of symptom distribution ($p>0.05$). (see Table 8 and Figures 3 and 4).

Table 5. Distribution of psychological symptoms in the two research groups before treatment

Severity of psychological symptoms before treatment	Selective Serotonin Reuptake Inhibitors		Combined Oral Contraceptives	
	moderate	Severe	moderate	Severe
Mood Swings	33 (50.8%)	32 (49.2%)	39 (59.1%)	27 (40.9%)
Irritability	37 (59.7%)	25 (40.3%)	38 (59.4%)	26 (40.6%)
Anxiety	35 (58.3%)	25 (41.7%)	39 (63.9%)	22 (36.1%)
Depressed mood	26 (45.6%)	31 (54.4%)	26 (47.3%)	29 (52.7%)
Appetite changes	24 (44.4%)	30 (55.6%)	24 (42.1%)	33 (57.9%)
Poor concentration	32 (57.1%)	24 (42.9%)	30 (56.6%)	23 (43.4%)
Sleep Disturbances	25 (54.3%)	21 (45.7%)	27 (55.1%)	22 (44.9%)

Table 6. Distribution of psychological symptoms in the two research groups after treatment

Severity of Physiological Symptoms after Treatment	Selective Serotonin Reuptake Inhibitors		Combined Oral Contraceptives	
	None	Mild	None	Mild
Mood Swings	59 (90.8%)	6 (9.2%)	55 (83.3%)	11 (16.7%)
Irritability	60 (96.8%)	2 (3.2%)	57 (89.1%)	7 (10.9%)
Anxiety	55 (91.7%)	5 (8.3%)	51 (83.6%)	10 (16.4%)
Depressed mood	57 (100%)	0 (0%)	49 (89.1%)	6 (10.9%)
Appetite changes	54 (100%)	0 (0%)	56 (98.2%)	1 (1.8%)
Poor concentration	52 (92.9%)	4 (7.21%)	45 (84.9%)	8 (15.1%)
Sleep Disturbances	45 (97.8%)	1 (2.2%)	44 (89.8%)	5 (10.2%)

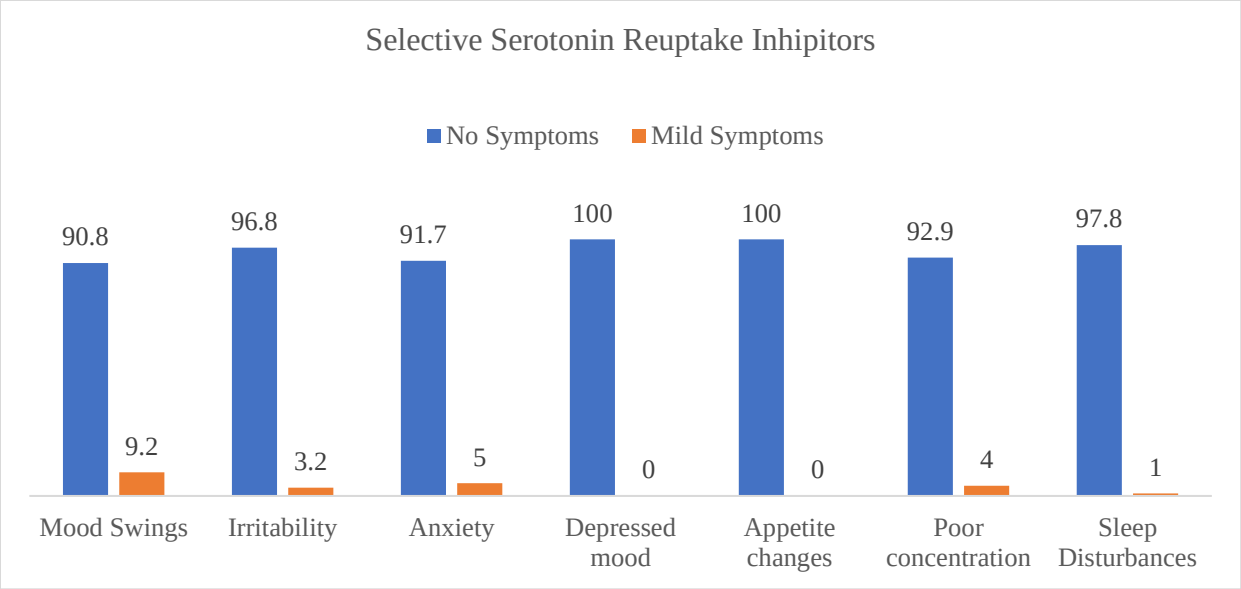

Fig. 1 Distribution of psychological symptoms in the two research groups after treatment with SSRIs

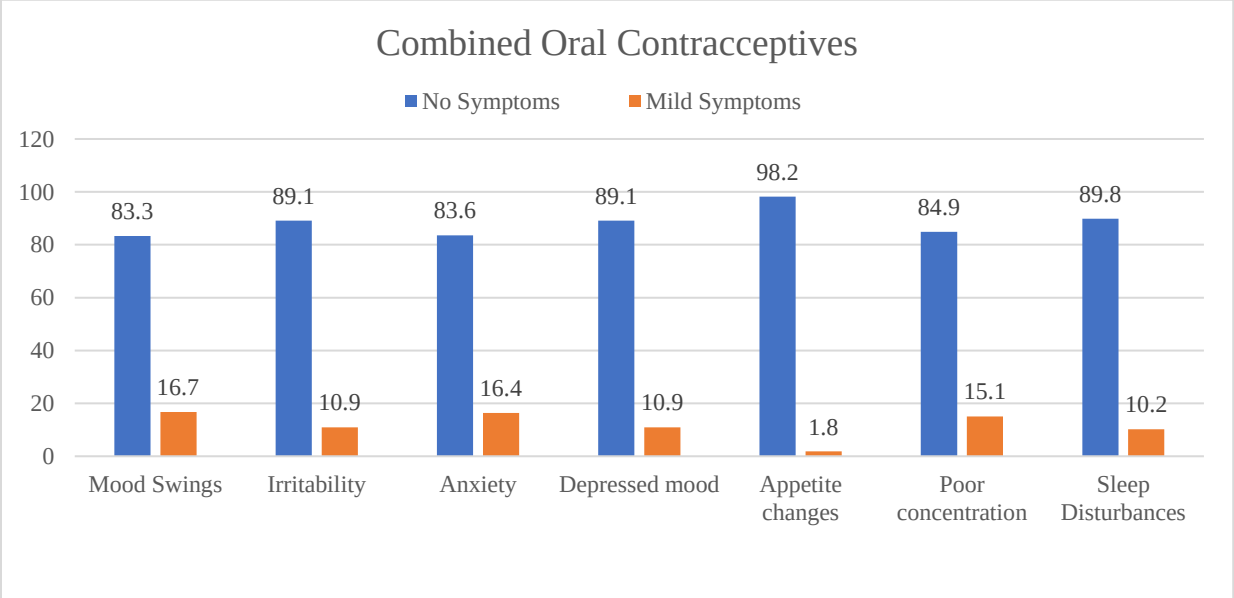

Fig. 2 Distribution of psychological symptoms in the two research groups after treatment with COCs

Table 7. Distribution of physical symptoms in the two research groups before treatment

Severity of Physical Symptoms before Treatment	Selective Serotonin Reuptake Inhibitors		Combined Oral Contraceptives	
	Moderate	Severe	Moderate	Severe
Abdominal bloating	40 (63.5%)	23 (36.5%)	44 (66.7%)	22 (33.3%)
Breast tenderness	33 (56.9%)	25 (43.1%)	31 (51.7%)	29 (48.3%)
Headache	20 (55.6%)	16 (44.4%)	23 (57.5%)	17 (42.5%)
Weakness	16 (41.1%)	23 (58.9%)	14 (40%)	21 (60%)
Skeletal pain	20 (58.8%)	14 (41.2%)	22 (59.5%)	15 (40.5%)
Dizziness	13 (52%)	12 (48%)	12 (54.5%)	10 (45.5%)
Hot flashes	9 (42.9%)	12 (57.1%)	10 (43.5%)	13 (56.5%)

Table 8. Distribution of physical symptoms in the two research groups after treatment

Severity of Physical Symptoms After Treatment	Selective Serotonin Reuptake Inhibitors		Combined Oral Contraceptives	
	None	Mild	None	Mild
Abdominal bloating	54 (85.7%)	9 (14.3%)	53 (80.3%)	13 (19.7%)
Breast tenderness	49 (84.5%)	9 (15.5%)	54 (90%)	6 (10%)
Headache	36 (100%)	0 (0%)	35 (87.5%)	5 (12.5%)
Weakness	36 (92.3%)	4 (7.7%)	30 (85.7%)	5 (14.3%)
Skeletal pain	32 (94.1%)	2 (5.9%)	36 (97.3%)	1 (2.7%)
Dizziness	22 (88%)	3 (12%)	20 (90.9%)	2 (9.1%)
Hot flashes	21 (100%)	0 (0%)	20 (86.9%)	3 (13.1%)

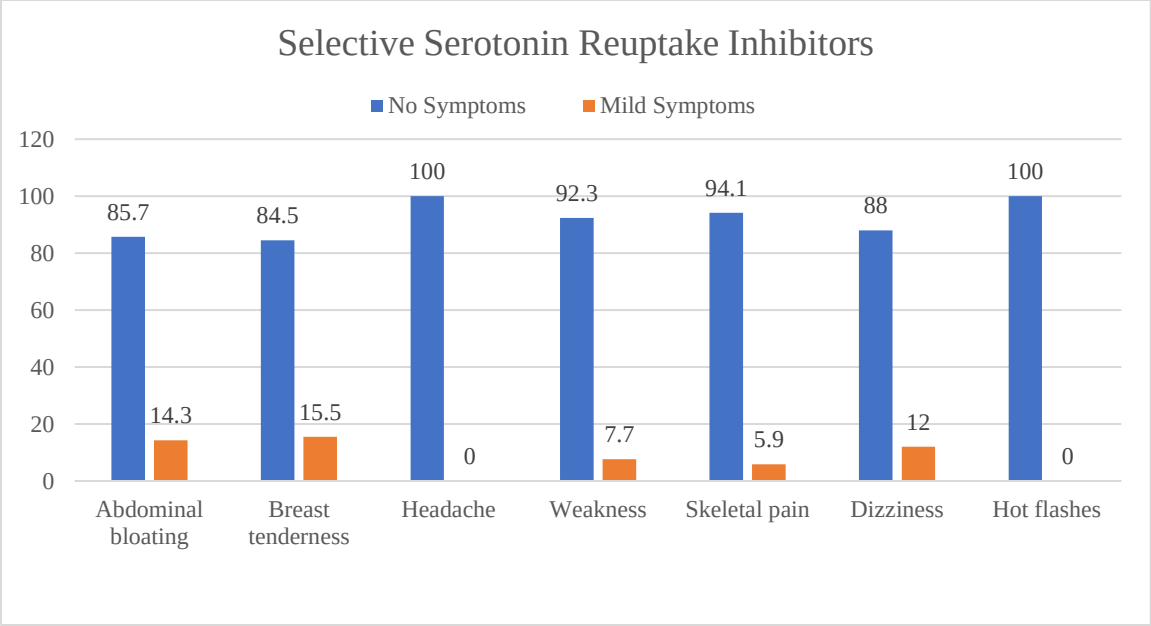

Fig. 3 Distribution of physical symptoms in the two research groups after treatment with SSRIs

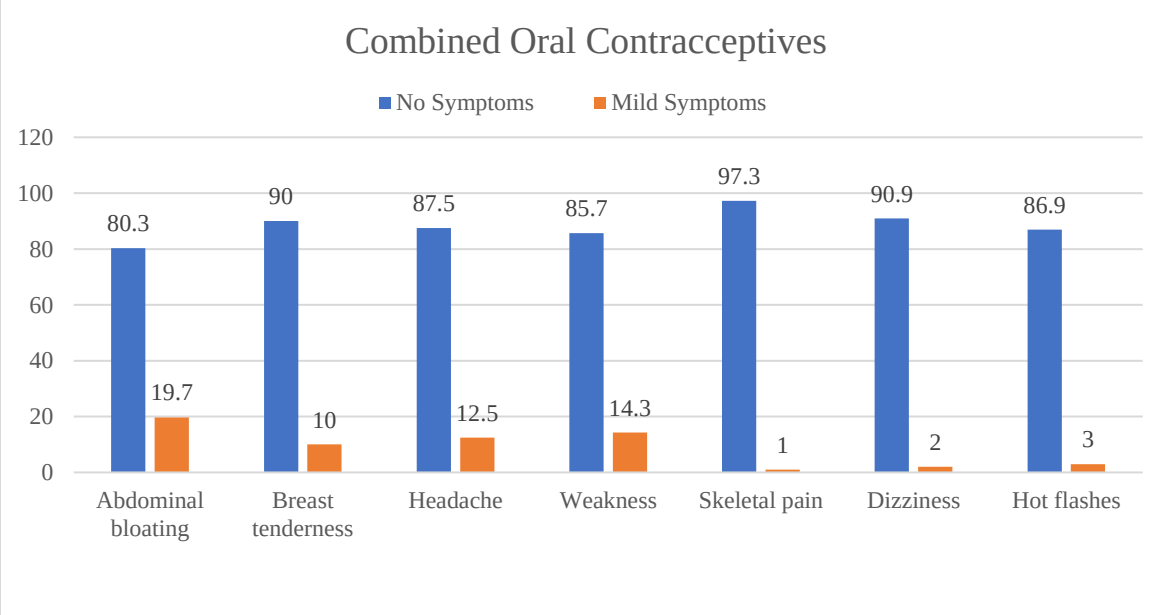

Fig. 4 Distribution of physical symptoms in the two research groups after treatment with COCs

3.4. Side Effects

Side effects for women who received treatment with serotonin reuptake inhibitors were as follows: Nausea 42.2% - Decreased libido 28% - Dry mouth 26.7% - Loss of appetite 16% (see Table 9).

Table 9: Side effects of serotonin reuptake inhibitors

Side Effects of Serotonin Reuptake Inhibitors	Number	Percentage
Nausea	32	42.7%
Decreased libido	21	28%
Dry mouth	20	26.7%
Loss of appetite	12	16%

Side effects for women who received treatment with oral contraceptives were as follows: Stomach pain 12% - Nausea 12% - Mood swings 10.7% - Headache 6.7% (see Table 10).

Table 10. Side effects of oral contraceptives

Side effects of combined oral contraceptives	number	percentage
Stomach pain	9	12%
Nausea	9	12%
Mood swings	8	10.7%
Headache	5	6.7%

4. Discussion

This study was conducted on 150 women who were diagnosed with premenstrual syndrome and who met the inclusion criteria for the study and consented to participate. The women were divided according to the treatment plan into two groups:

- The first group received treatment with combined oral contraceptive “Drospirenone 3 mg and ethinyl estradiol 20 mcg” (75 women).
- The second group received treatment with selective serotonin reuptake inhibitor “Escitalopram 10 mg” (75 women).
- Clinical symptoms and final outcome of treatment were compared between the two research groups.

The study revealed the following findings:

The most frequent age group was 30-35 years, and this may be explained by the fact that women in this age group may suffer from anxiety and mood disorders more frequently than younger or older women due to the more common family responsibilities at these ages that are associated with distress. Psychological problems lead to an increased risk of the syndrome, as well as some habits prevent young women from talking about health issues related to menstruation.

No statistically significant differences were observed between the two research groups regarding the distribution of physical and psychological symptoms (P>0.05).

The physical and psychological symptoms ranged in severity before treatment from moderate to severe in both groups. After applying the treatment, the symptoms disappeared completely for the vast majority of women in both groups and became mild for the remaining percentage of women.

Improvement in psychological symptoms was more noticeable in the “selective serotonin reuptake inhibitor” treatment group.

- The mechanism of SSRIs in alleviating the symptoms of premenstrual syndrome is due to raising the level of the neurotransmitter serotonin in the brain. For contraceptives, their mechanism of action is due to inhibiting ovulation and thus inhibiting the effect of ovarian hormonal changes on the work of neurotransmitters.
- Nausea and loss of libido were the most frequently observed side effects in the SSRI group, and headache and nausea were the most frequently observed side effects in the combined contraceptive group.

In comparison with other studies:

Kimberly et al. (2005) USA

- The average age of patients was 31 years.
- A statistically significant improvement in mood symptoms, physical symptoms and behavior was observed in the treatment group.
- Response (defined as 50% improvement in symptoms) was higher in the treatment group compared with placebo (48% vs. 36%, p:0.01).
- Compared with the current study the number of patients is smaller in the current study, and the average age of the patients is lower.
- Improvement in psychological and physical symptoms was observed after treatment with combined contraceptives in both studies. [5]

Anouk et al. (2021) Netherlands (Meta-Analysis)

- The average age across all studies was in the range from 24 to 36 years.
- Treatment improved PMS symptoms except for low mood, which did not improve.
- No differences were observed regarding the final yield between the different compounds.
- Compared to the current study, the number of patients was smaller in our study, with similar ages for the women, and treatment with combined contraceptives led to an improvement in psychological symptoms in our study in contrast to this study.
- No comparison with SSRIs was made in this study.[6]

Siyan et al. (2023) New Zealand

- Treatment resulted in an improvement in symptoms and functional impairment related to productivity and social activities.
- The percentage of side effects resulting from the use of contraceptive compounds ranged from 6-16%, which included nausea, breast pain, and bleeding between menstrual cycles.
- Compared to the current study, the number of patients was smaller in our study, and both studies were similar in the effectiveness of treatment in alleviating symptoms, with the occurrence of some side effects. [7]

Eriksson et al (2008) Sweden

- The average age was 36 years
- A decrease in the VAS scale for each (agitation, low mood, and anxiety) was observed in the three groups, but clearly with the higher dose
- Nausea was the most frequent symptom, followed by fatigue and decreased libido
- Compared with the current study, the number of women was similar, but only one type of treatment (SSRIs) with different doses without combined contraceptives was applied, with a lower average age in our study.
- Both studies were similar in that symptoms improved after treatment, with nausea being the most frequent side effect [8]

Shah et al (2008) USA

- These compounds have shown effectiveness in treating premenstrual syndrome.
- The intermittent dosing regimen was less effective than continuous treatment.
- No differences were observed in the final result depending on the type of compound.
- The difference with the current study is the larger number of patients, the use of different compounds for treatment, and the lack of comparison with combined contraceptives. The two studies were similar in the improvement of symptoms of the syndrome after treatment. [9]

Jane et al. (2021) New Zealand (Meta-Analysis)

- The age of women in the majority of studies ranged from 18-49 years (except for one study, 15-19 years).
- These compounds have shown effectiveness in eliminating symptoms whether taken intermittently in the luteinizing phase or continuously.
- There was withdrawal from the study due to side effects, the most frequent of which were
- Nausea, drowsiness, fatigue, decreased libido, and sweating were more pronounced at higher doses.
- Medium doses of these compounds were the most effective, although smaller doses showed specific efficacy.
- Compared with the current study, the incidence of disease was lower in our study, with a lower mean age, and no comparison was made with combined contraceptives.
- Both studies were similar in the effectiveness of these compounds in eliminating the symptoms of the syndrome, and nausea was the most frequent side effect. [10]

5. Conclusion

Both combined oral contraceptives and SSRIs can be used in the management of moderate to severe Premenstrual Syndrome (PMS) with similar efficacy.

Combined oral contraceptives can be used in married women who suffer from the syndrome and desire to prevent pregnancy.

It is recommended to conduct future studies that include a larger number of patients and in several centers, comparing the effectiveness of previous therapeutic methods and different doses in alleviating the symptoms of premenstrual syndrome, as it is a common problem with a significant burden on the individual and societal levels.

Acknowledgments

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