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Is Administration of Depot Medroxyprogesterone Acetate Injections Every Three Months Effective in Decreasing Pain Associated with Endometriosis in Premenopausal Women?

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Is Administration Of Depot Medroxyprogesterone Acetate Injections Every Three Months Effective In Decreasing Pain Associated With Endometriosis In Premenopausal Women?

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ABSTRACT

OBJECTIVE: The objective of this systematic EBM review is to determine whether or not the administration of depot medroxyprogesterone acetate injections every three months are effective in decreasing pain associated with endometriosis in premenopausal women.

STUDY DESIGN: A review of two randomized controlled trials and one randomized comparative trial comparing pain improvement from depot medroxyprogesterone acetate (DMPA) injections at different time intervals and/or in comparison to other hormonal birth control methods in premenopausal patients suffering from endometriosis.

DATA SOURCES: Randomized controlled trials and a randomized comparative trial were found using PubMed and Ovid MEDLINE databases.

OUTCOME MEASURED: Outcomes were measured for reduction of pain by a verbal rating scale and/or a 10-cm or a 100-mm visual analog scale.

RESULTS: Wong et al found that the pain score was significantly reduced all through the study period as long as the therapy of 150mg DMPA intramuscular injection every three months was continued (in all patients but one). Both Cheewadhanaraks et al and Walch et al showed a decreased in pain scores with DMPA in comparison to the control, but neither article calculated statistics comparing these scores to the baseline, therefore results are inconclusive whether or not pain associated with endometriosis is decreased with administration of DMPA injections every three months in premenopausal women.

CONCLUSION: Based on the articles reviewed, one of the articles showed evidence that 150mg injections of DMPA administered every three months is an effective means of decreasing endometriosis-associated pain in premenopausal women. The other two articles had inconclusive results, therefore further research is warranted.

KEYWORD: Depot Medroxyprogesterone Acetate, DMPA, Endometriosis

INTRODUCTION

Endometriosis is a chronic and recurrent condition where endometrial tissues grow in areas of the body outside the uterus leading to pelvic pain, dysmenorrhea, and infertility.[1] Normally each month the cells lining the uterus increase in thickness following the release of hormones from the ovaries. These cells then shed from the endometrial lining during a woman’s menstrual period. If instead the endometrial cells implant outside the uterus, endometriosis occurs resulting in tissue implanting in various organs in the pelvic region. This misplaced tissue is not shed monthly but it stays in place and grows during menstruation thereby frequently causing cyclic bleeding, scarring, and dysmenorrhea.[2]

It is estimated approximately 6-20% of reproductive-age women[1] are affected by endometriosis thereby afflicting approximately 167 million women worldwide and 8.5 million in North America[4]. The prevalence of endometriosis is assumed to be around 10% of women of reproductive age[3, 5] making it a prominent concern for healthcare providers. The average cost of endometriosis is $12,500/year per woman ($8,200 lost in work productivity; $4,000 for direct health care costs). Costs were higher with increasing severity of disease and the presence of dysmenorrhea[6], although they may vary according to socioeconomic status and individual insurance policies regarding coverage of treatment options. In the United States alone, endometriosis-associated costs are estimated to be $22 billion annually.[4] Yearly healthcare visits vary, however a woman with endometriosis sees 4-5 doctors prior to being correctly diagnosed.[6]

This estrogen-dependent condition is most commonly associated with dysmenorrhea but it may also cause dyspareunia, infertility, fatigue, dysuria, pain during bowel movements, and other gastrointestinal symptoms.[1, 6] Endometriosis is usually diagnosed between 25-35 years of age although the condition is thought to have developed around the beginning of a girl’s

menstrual cycle. Women with a family history of the condition, who never had children, developed their period at a young age, have frequent or long periods, or have a closed hymen are more likely to develop endometriosis.[2] The cause of endometriosis is unknown; however, the retrograde menstruation theory proposes that during a woman’s cycle part of the menstrual tissue backs up through the oviducts then implants and grows in the abdomen. There are theories that this tissue is sent from the uterus to other body parts via the lymph or blood system.[6] Additionally, it has been proposed that stem cells, genetics, dysfunctional immune responses, and environmental sources all may contribute in some way to this multi-factorial condition.[4]

Pain medication, hormonal therapy, surgery, traditional Chinese medicine, nutritional changes, homeopathy, allergy control, and immune therapy are all treatment options for endometriosis, as there is no cure.[6] Treatment depends on age, severity of symptoms and disease, and whether a woman wants to become pregnant in the future.[2] Mild symptoms may be managed with exercise, relaxation techniques, and non-steroidal anti-inflammatory drugs (NSAIDs). In order to halt the disease progression, hormone medications have been shown to reduce most symptoms.[2] The gold standard for women who have no improvement with other treatment methods and are still experiencing severe pain is pelvic laparascopic excision surgery to remove all endometrial implants and adhesions.[2, 4] Hysterectomy, including ovary removal of ovaries, is a last resort for persistent symptoms in women who do not wish to have future children.[2]

For many women with moderate and severe endometriosis, they still run a high risk of symptoms associated with the disease after conservative surgery. Studies have shown that hormonal therapies are equally effective in the control of endometriosis-associated pain, but their side effects and costs differ.[7] Because hormonal therapy is less invasive and more affordable

than surgery and often offers less systemic side effects than antiestrogrens[1], many hormonal methods have been utilized to determine their effect on endometriosis-associated dysmenorrhea.

Depot medroxyprogesterone acetate (DMPA), a birth control drug, is a 17-hydroxy derivate progestogen with moderate androgenic activity that is administered intramuscularly in attempt to decrease endometriosis-associated pain. This paper evaluates three randomized controlled/comparative trials comparing the effectiveness of DMPA injections every three months in decreasing endometriosis-associated pain in premenopausal women. This systemic review compares DMPA injections given every three months to DMPA administered every month for six months followed by every three months, a levonorgestrel-releasing intrauterine system, and a single-rod etonogestrel-containing contraceptive implant.[1, 3, 7] All regimens are primarily hormonal birth control methods.

OBJECTIVE

The objective of this systematic review is to determine whether or not the administration of depot medroxyprogesterone acetate injections every three months are effective in decreasing pain associated with endometriosis in premenopausal women.

METHODS

The population selected for this study included premenopausal women between the ages of eighteen and fifty years old who were experiencing endometriosis-associated pain. The intervention applied in the systemic review was 150mg DMPA intramuscular injection given every three months. The comparisons were to 150mg DMPA intramuscular injection administered every month for six months followed by every three months, a levonorgestrel-releasing intrauterine system (Mirena), a single-rod etonogestrel-containing contraceptive implant (Implanon).[1, 3, 7] The outcome measured is reduction of pain and was evaluated by a

verbal rating scale and a 10-cm or a 100-mm visual analog scale according to specific criteria. The types of studies included three randomized controlled/comparative trials.

A detailed literature search was conducted using PubMed and Ovid MEDLINE. The searches were conducted from December 2011 until December 2012. The keywords searched for were “Medroxyprogesterone Acetate”, “Depoprovera”, and “Endometriosis”. Each article was published originally in English in peer reviewed journals. The articles were researched and selected based on relevance and patient oriented outcomes that matter to them (POEMS). Inclusion criteria are composed of studies that were randomized controlled/comparative trials that included POEMS and administered a DMPA dosage of 150mg. Exclusion criteria include articles with patients under the age of eighteen and over the age of fifty years old and those that were published prior to 2009. Statistics reported or used include p-value, baseline median, 95% confidence interval (CI), student t-test, Experimental Event Rate (EER), Controlled Event Rate (CER), Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI), and Numbers Needed to Treat (NNT). Table 1 includes the demographics of the studies analyzed in this review.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Participants	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cheewadhanaraks et al (2009)	RCT	112	18-46 years	Premenopausal women from 18 to 46 years of age who had endometriosis-associated pain for at least 6 months and did not wish to conceive in the next 2 years or more	Medical therapies for endometriosis other than NSAIDs within last 6 months; contraindications to DMPA; request for extirpative surgery; ovarian endometioma >2cm; other pelvic pathology; GI, urologic, or orthopedic diseases	42	150 mg DMPA injections every month for 6 months then every 3 months for 15 months or every 3 months for 15 months
Walch et al (2009)	RCT	41	22-44 years	Women with symptomatic Stage I-IV endometriosis proven by laparoscopy or laparotomy prior to inclusion; dysmenorrhea and	Desire to conceive; + hCG test; suspicious Pap; uterine or adnexal anomalies endometriosis; large adenomas; any malignancy; performed hysterectomy, C/I to	11	Implanon (subdermal implantation) or 150 mg DMPA injections every 3 months

				menstrual irregularities associated with endometriosis and no desire to conceive within the next 12 months; pre-menopausal; grade severity of dysmenorrhea, nonmenstrual pelvic pain, dyspareunia on a 100-mm visual analog scale with a mean score >50 over a period of 14 days, including one menstrual bleeding	progestins; use of an oral contraceptive pill within 1 month; l use of injectable hormonal treatments during the last 3 months before study		
Wong et al (2010)	RCT	30	≥ 30 years	Premenopausal patients age ≥30, history of surgery performed in past 5 years for moderate or severe endometriosis; no evidence of lesion recurrence or osteoporosis from a DEXA scan on lumbar spine/hip; no desire for pregnancy within 3 years; patient agreed to hormonal therapy	None given	10	Mirena (LNG-IUS) or 150 mg MPA every 3 months

OUTCOMES MEASURED

All outcomes measured were based on relevance to Patient Oriented Evidence that Matters, or POEMS. Although all three of the studies had multiple POEMS, this systematic review focuses specifically on the outcome of pain associated with endometriosis. One of the articles measured pain on a verbal rating scale from 0-3 (0 – no pain, 1 – mild pain not requiring intervention, 2 – moderate pain requiring analgesics, 3 – intolerable pain).[7] The second article measured pain using a 100-mm visual analog scale where a score higher than fifty over a fourteen day period was necessary for inclusion.[1] The third article utilized both a verbal rating scale from 0-3 (0 – no pain, 1 – no absence from work but decrease efficiency, 2 – absence from

work <1 day per cycle, 3 – absence from work ≥ 1 day per cycle) and a 10-cm visual analog scale from 0-10 (0 – absence of pain, 10 – unbearable pain) to measure pain.[3]

RESULTS

All three articles presented in this systematic review are randomized controlled/comparative trials that compare 150mg of DMPA intramuscular injections every three months to other birth control methods or DMPA administered during different time intervals to determine its efficacy at decreasing endometriosis-associated pain in premenopausal women.[1, 3, 7]

Wong et al conducted a randomized controlled trial comparing levonorgestrel-releasing intrauterine system (LNG-IUS, or Mirena) to DMPA as long-term maintenance therapy for patients with moderate and severe endometriosis. The study began with thirty premenopausal patients ≥30 years of age with history of conservative surgery performed within five years for moderate to severe endometriosis, no evidence of lesion recurrence or osteoporosis from a DEXA scan on the lumbar spine or hip, no desire for pregnancy within three years, and the patient agreed to receive hormonal therapy. There were no exclusion criteria. Fifteen of the women were randomized into the LNG-IUS group and fifteen into the DMPA group.[7]

The women in the LNG-IUS group had the product inserted into the uterus where it released levonorgesterol at a rate of 20 ug/24 hrs for up to five years at a virtually constant rate. The 150mg DMPA intramuscular injections were administered every three months for three years. Follow up in the first year was every three months, followed by every six months in the second and third years. Zero patients were lost to follow-up although ten patients discontinued the interaction due to adverse side effects – two from the LNG-IUS group and eight from the DMPA group. As a result, the LNG-IUS had a better compliance rate.[7]

After initiation of treatment, there was a decrease in the pain scores three months later with both LNG-IUS ($p<0.02$) and DMPA ($p<0.002$), as well as a decrease throughout the rest of the study for all patients except one on DMPA. As shown in Table 2, there was a change in the mean from the baseline for LNG-IUS of 1.5 and DMPA of 1.2. At thirty-six months, LNG-IUS was found to be significantly lower in pain scores versus DMPA although no statistics were reported. Overall, the pain score throughout the study between the two variables was statistically significant with a p-value of <0.025. Both the control and intervention were found to be effective in decreasing pain associated with endometriosis when compared to the baseline pain level.[7]

Table 2: Summary of Pain Scores Over 36 Months

	# of Patients	**Pain Score Change in Mean From Baseline**	**Pain Score p-value from Baseline-3mo**	**p-value at 36mo between LNG-IUS and Depot MPA**
LNG-IUS	15	1.5 (1.6-0.1)	<0.02	<0.025
Depot MPA	15	1.2 (1.9-0.7)	<0.002	<0.025

*Statistical comparison was by Student *t* test

Walch et al conducted a randomized controlled trial comparing the therapeutic efficacies of Implanon, a single-rod etonogestrel-containing contraceptive implant administered intradermally to prevent ovulation for at least three years, and 150mg DMPA intramuscular injections every three months in relieving pain associated with endometriosis in premenopausal women. The study began with forty-one premenopausal patients between 22-44 years of age with symptomatic endometriosis who had no desire to conceive in the next twelve months and had a mean VAS score >50 over fourteen days including one menstrual bleeding. Patients were excluded with a desire to conceive, a positive hCG test, a suspicious Pap smear, uterine or adnexal anomalies, large adenomas, any malignancy, performed hysterectomy, contraindications to progestins, oral contraceptive pill usage within one month, or injectable hormonal treatments during the last three months before study entry. Eleven women withdrew due to adverse side

effects, the desire to conceive, or a dwelling change – four from the Implanon group and seven from the DMPA group, but this dropout rate was not considered statistically significant.[1]

During the one year study, there was a marked reduction in pain intensity after administration of both Implanon and DMPA. This study focused its primary outcome measure in regards to pain reduction at the six month mark when compare to baseline.[1] Since the dichotomous data was given, the control event rate (CER), experimental event rate (EER), absolute benefit increase (ABI), relative benefit increase (RBI), and number needed to treat (NNT) were calculated. The CER is the percentage of patients receiving Implanon whereas the EER is those receiving DMPA. The ABI is the increase of a good event as a result of DMPA. The RBI is the proportional increase in the rate of good outcomes between the Implanon and DMPA groups. The number needed to treat determines the number of people needed to be treated in order to prevent one patient from experiencing pain associated with endometriosis.

The mean decrease in VAS scores (quantifying pain intensity) after the first six months was 68% with a 95% CI (53-83) for the Implanon group and 53% with a 95% CI (28-79) in the DMPA group. The NNT value was -6 signifying that for every six patients treated with Implanon, one less patient experienced pain associated with endometriosis compared to DMPA, as shown in Table 3. The difference between these two groups was not shown to be statistically significant with $p=0.36$, where significance was achieved when $p<0.05$. On month six, the VAS score for the Implanon group was not statistically significant compared to the DMPA group with $p=0.69$. There was no statistical difference in VAS scores between treatment groups when analyzed ($p=0.8$). When comparing Implanon to DMPA, the difference in VAS scores was not statistically significant. When compared to baseline, each regimen individually showed a marked decrease in pain scores although analysis was not performed making the data inconclusive.[1]

Table 3: Analysis of Pain Reduction at 6 Months in Relevance to RBI/ABI/NNT

	Controlled Event Rate (CER)	**Experimental Event Rate (EER)**	**p-value**	**Relative Benefit Increase (RBI)**	**Absolute Benefit Increase (ABI)**	**Numbers Needed to Treat (NNT)**
Walch et al	0.68	0.53	p=0.36	0.221	-0.15	-6

Cheewadhanaraks et al conducted a randomized comparative trial comparing 150 mg DMPA intramuscular injections every month for six months then every three months for fifteen months (regimen A) to injections every three months for fifteen months (regimen B) to determine the optimal interval in the long-term treatment in pain associated with endometriosis. Patients were seen for a follow-up visit every three months. The study was conducted with 112 premenopausal women 18-46 years of age who had endometriosis-associated pain for at least six months and did not wish to conceive in the next two years or more. Exclusion criteria included medications for endometriosis besides NSAIDs within last six months, contraindications to DMPA, extirpative surgery request, ovarian endometioma >2cm (ruled out with transvaginal ultrasound), other pelvic pathology, or known GI, urologic, and orthopedic diseases. In the two months prior to the study, an initial laparoscopic diagnosis of endometriosis was performed and staged according to the American Fertility Society classification system. Forty-two women withdrew from the study, twenty-one from each regimen, due to persistent pain and adverse side effects. This was not statistically significant since p=0.032 ($p<0.05$ was considered significant).[3]

Throughout the fifteen month study, there was a continual trend resulting in a decrease in the pain scores between patients in both treatment regimens. At the six month time interval, there was statistical significance achieved where there was a larger decrease in pain in regimen A in comparison to regimen B as seen in Table 4. This table also shows the verbal rating scores (VRS) during the six month time interval that was analyzed and found to be statistically significant being the p-values were <0.05. Regardless of this outcome, there were no statistics

conducted comparing pain scores from either regimen to baseline pain before beginning the study. Therefore, although statistical significance was achieved at the sixth month time interval when comparing regimen A to regimen B, in terms of answering the proposed question of this review the results would have to be considered inconclusive due to lack of statistical analysis.[3]

Table 4: Verbal Rating Scale for Pain Intensity

	0	**1**	**2**	**3**	**p-value**
Regimen A	35	8	0	0	0.012
Regimen B	26	12	6	1	0.009

DISCUSSION

All three studies showed a decrease in pain scores in comparison to the control in each study, although Walch et al is the only study that showed statistical significance in reduction of pain scores from DMPA when compared to baseline. DMPA is widely available with a prescription from a healthcare practitioner. Most insurances that cover the birth control pill cover the MDPA shot as well, although this can vary per individual. For those without insurance, Planned Parenthood offers the shot at a discounted rate.[8] DMPA is contraindicated in patients with pregnancy or as a diagnostic test for pregnancy, thrombophlebitis, thromboembolic disorders, cerebral vascular disease, breast malignancy, hypersensitivity to DMPA, liver disease, or undiagnosed vaginal bleeding. Warnings and precautions of the drug include loss of bone mineral density, thromboembolic disorders, cancer risks, ectopic pregnancy, anaphylaxis, liver disturbances, convulsions, depression, bleeding irregularities, weight gain, carbohydrate metabolism reduction, fluid retention, delayed fertility, and sexually transmitted diseases.[9]

The black box warning notes that DMPA causes increased osteoporotic effects the longer it is administered, may remain after the injections cease, and may be irreversible. Pfizer, the DMPA drug manufacturer, and the Food and Drug Administration advise that it should not be used over a two year period unless no other options are feasible due to bone loss concerns. It is

primarily used as a progestin hormone birth control method to prevent pregnancy. It causes a change in menstrual periods of most women where they experience an increase or decrease in flow, increased spotting, or amenorrhea.[9] DMPA is also being used in nine states as a form of chemical castration where it acts as a sexual suppressant in male sex offenders.[10]

All three of the articles reviewed had limitations to the studies which included small sample sizes with significant drop out rates and no blinding. If the study sizes were larger, it is possible that the results may have been different. In the future, it may be of interest to administer DMPA injections to one group and placebo shots to another group, as long as the women involved did not have concerns about becoming pregnant. This way both the patients and the shot administrators would be unaware of which injection each woman was receiving making it a double blinded study. It would also be helpful to perform statistical analysis on the decrease in pain levels when compared to the baseline. This would show the effectiveness of each drug individually, in addition to the comparison to other methods if warranted in the particular study.

CONCLUSION

According to the three articles selected for this systemic review, Walch et all showed that the administration of depot medroxyprogesterone acetate injections every three months is effective in decreasing pain associated with endometriosis in premenopausal women.[1] Wong et al and Cheewadhanaraks et al were found to be inconclusive. Although, all studies showed a significant decrease in pain levels when compared to the control, the latter two studies did not publish data comparing DMPA pain levels throughout the study to the initial baseline measurements. Future study is warranted using a larger double blinded multicultural study that looks at the administration of DMPA to a placebo and calculates statistical analysis on pain reduction for the drug throughout the study in comparison to baseline.

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