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Influence of Parenteral Progesterone Administration on the Prevalence and Severity of Mastodynia in Active Duty Servicewomen: A Multi-institutional Case-control Study

MAJ David M. Ehuus

Tripler Army Medical Center
Honolulu, HI 96859-5000

U.S. Army Medical Research and Materiel Command
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Progestosterone has been proposed as a treatment for mastalgia but the literature supporting their use is conflicting and currently inconclusive. The prevalence and severity of mastalgia in women receiving parenteral progestrone for contraception was compared to that of a randomly selected age-matched control group using a validated survey instrument. Surveys were mailed to 1,320 case subjects, recruited from 11 Army Medical Treatment Facilities, and 6,667 randomly selected age-matched control subjects. 9.3% of women taking Depo-Provera® reported frequent breast pain as compared to 20.8% of control subjects (P < 0.001). This reduction in breast pain prevalence was sustained across all age ranges. The prevalence of moderate - severe breast pain, (i.e. pain likely to require some form of treatment) was 2.3% in the Depo-Provera® group as compared to 4.9% in the control group (P < 0.02). A non-cyclic pattern of breast pain predominated in the Depo-Provera® group (78.8%), while cyclic breast pain was more common in the control group (67.7%, P < 0.001). The overall prevalence and severity of non-cyclic breast pain was similar in both groups. Depo-Provera® effectively suppresses cyclic mastalgia in reproductive-age women. This medication does not pose the risk of endometrial cancer associated with Tamoxifen, nor does it have the virilizing or teratogenic effects of Danazol, thus it may represent optimal hormonal therapy for premenopausal women with moderate to severe breast pain.

Defense Women's Health
Mastalgia, Depo-Provera, Progesterones, Cross-sectional
Prevalence, Validated Survey, Breast Pain Severity

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DATA QUALITY INSPECTED 3
INTRODUCTION

Approximately 30% of women presenting to surgical breast clinics present for symptoms of breast pain\textsuperscript{1}. While approximately 85% of these women are adequately managed by reassurance alone, 15% will find that the breast pain poses intolerable life-style limitations\textsuperscript{2}. Therapies for intractable mastalgia are generally directed at altering the hormonal milieu of the breast, but none is completely reliable and all are currently under close scrutiny.

The specific physiologic and mechanical causes of breast pain are unclear at this time. A growing body of literature, however, suggests that excess estrogen effect at the level of the breast ductules and lobules is a central feature. Estrogen is produced by a maturing ovarian follicle each month. The corpus luteum, which remains after rupture of the follicle, produces progesterone during the later half of the cycle. Estrogen stimulates proliferation of the ductal epithelial cells, while progesterone stimulates differentiation of the lobules. Estrogen drives the proliferative response, while progesterone organizes and subdues it. It has been postulated that when this delicate balance shifts towards a relative estrogen excess, breast pain and nodularity result.

As a group, patients with benign breast disease have higher serum estrogen/progesterone ratios than women without symptoms of breast disease\textsuperscript{3}. While this alteration is sometimes the result of an absolute estrogen excess\textsuperscript{3,4}, it more frequently represents diminished progesterone levels (so called "luteal insufficiency")\textsuperscript{5,6,7}.

Progesterone administration represents a very direct way to shift the estrogen/progesterone ratio in favor of progesterone. Physiologic and biochemical effects of progesterone include inhibition of ovarian steroidogenesis through gonadotropin blockade, decreased estrogen receptor synthesis, increased estrogen degradation and improved translocation of the progesterone receptor into the nucleus.

One of the earliest trials of progesterone in the treatment of benign breast disease demonstrated symptomatic improvement in 96% of 234 women with mastalgia\textsuperscript{3,8}. In this uncontrolled study, a total of 260 women with various forms of benign breast disease were treated with topical progesterone cream and oral Lynestrenol (3-deoxy-17-ethynyl-nortestosterone) at 10 mg per day on days 10 - 25 of the menstrual cycle. Symptomatic improvement was correlated with a decrease in breast nodularity on palpation, but no improvement in the mammographic appearance of the breasts. A second, smaller Lynestrenol trial also demonstrated symptomatic improvement in 96% of 26 women with mastalgia\textsuperscript{9}. A recent uncontrolled trial comparing lynestrenol with two dosage levels of a
more potent progesterone (promegestone) found a 92.4% improvement rate in the
 lynestrenol group\textsuperscript{10}. The promegestone group experience a similar improvement rate. The
 only placebo-controlled trial of this drug included 160 patients and recorded an 82.1%
symptomatic improvement rate in the treatment arm as compared to 36.8% in the placebo
arm\textsuperscript{11}.

A variety of progesterone medications have been evaluated for the treatment of
mastalgia. Among these is a progesterone ointment which was popularized in France.
While an uncontrolled trial demonstrated improvement in 87% of 52 patients\textsuperscript{12}, a double-
blind, placebo-controlled, cross-over trial involving 25 patients failed to document any
effect\textsuperscript{13}. In contrast, treatment with a 2.5% progesterone vaginal cream resulted in a >
50% reduction in analog pain scale scores in 64.9% of 40 treatment arm patients as
compared to 22.2% of a placebo arm (P < 0.01)\textsuperscript{14}.

The most commonly prescribed progesterone in the United States is
medroxyprogesterone acetate (Provera\textsuperscript{®}). This agent was assessed in a small (N = 18
evaluable patients) randomized prospective trial and found to be ineffective for mastalgia
when administered in a dose of 10 mg per day on days 10 - 26 of the menstrual cycle\textsuperscript{15}.

The literature describing progesterone supplementation for the treatment of
mastalgia is confusing. The studies are generally small and uncontrolled, and questions
of medication compliance are not addressed. In addition, it is difficult to compare results
between studies because so many different progesterone preparations are used. The use of
progesterones for the treatment of mastalgia remains controversial, but commonly practiced
in some settings.

The current study employs a validated survey instrument to measure the prevalence
and severity of breast pain in women receiving long-term progesterone supplementation for
contraception. These results were compared with those of an age-matched control
population. This study was designed to 1) provide evidence for or against a role for
progesterones in the treatment and prevention of mastalgia, 2) estimate the impact of
mastalgia on productivity and readiness in our active duty servicewomen, and 3) provide
some insight into current perceptions of the quality of medical care available for mastalgia
patients.

METHODS

General Study Design

The prevalence and severity of mastalgia in 346 women receiving parenteral
progesterones for contraception was compared to that of 1,150 randomly selected age-
matched control subjects using a validated survey instrument. Women between the ages of 18 and 44 years, receiving Depo-Provera® injections for contraception, were enrolled at 11 Army OB/GYN or Family Medicine clinics evenly distributed across the United States. Informed consent was required because demographic data was retained on these women. Approximately 30 days following Depo-Provera® administration the study instrument was mailed to the volunteers. If the completed questionnaire was not received within 30 days, a second, and then a third questionnaire was sent. Only questionnaires that were completed within 90 days of the Depo-Provera® injection were retained. Age-matched controls (+/- 6 months) were randomly selected by Michigan-based Vector Research, and current addresses were appended from the Defense Information System Database (DMIS) in Monterey, California. Questionnaires were mailed to control subjects in three large batches. The study instrument was produced using ScanBook® and scored using a Scantron 8200 optical mark reader. Each line of data was manually inspected for accuracy.

**Questionnaire Design and Validation**

The questionnaire was designed to measure the prevalence, severity and pattern (cyclic or non-cyclic) of mastalgia and to assess satisfaction with the medical evaluation and treatment provided for breast pain. Confounding variables are accounted for with questions concerning hormonal medication usage, variations in body size, early or surgical menopause, pregnancy or lactation, and recent breast surgery. The questionnaire also contains several question repeats to document internal consistency.

Questionnaire development and validation was accomplished in the surgical breast clinic at Tripler Army Medical Center, where women between the ages of 18 and 44 were interviewed and examined by the Principal Investigator (P.I.) after completing a questionnaire. The questionnaire, in its final form, was administered to 84 consecutive patients. After completing a questionnaire each patient was evaluated by the P.I. to distinguish breast pain from chest wall pain, cyclic pain from non-cyclic pain, and pain requiring medical intervention from that more appropriately treated by reassurance alone. In addition, information was gathered to document the reliability of reporting of confounding variables such as hormonal medication usage, early or surgical menopause, pregnancy or lactation, and recent breast surgery. Accuracy of reporting was measured for each variable by correlating the response recorded in the survey with that obtained by the examiner. Cyclic pain was distinguished from non-cyclic pain using three questions which addressed the frequency of breast pain
and its relationship to menstrual periods. Various combinations of these responses were compared to identify the combination that correlated best with the examiner's assignment of cyclic or non-cyclic mastalgia.

Seven questions addressed four aspects of breast pain severity: 1) visual analog pain scale (VAPS), 2) duration of pain, 3) interference with usual activities, and 4) medication usage. Responses were scored as follows:

1) VAPS score is the integer nearest to the pain scale mark (ranging from 1 for minimal pain to 10 for severe pain.

2) Duration Score
   1 - 1 - 2 days
   2 - 3 - 6 days
   3 - at least 1 week, but less than 2 weeks
   4 - ≥ 2 weeks

3) Interference with Activities Score
   1 - performed usual duties in usual fashion
   2 - worked with modification: worked slower, took more frequent breaks, avoided certain activities
   3 - missed part or all of one duty day
   4 - missed more than one duty day

4) Medication Score
   1 - none
   2 - over the counter aspirin, Tylenol or ibuprofen
   3 - prescription strength ibuprofen or naprosyn or other NSAIA
   4 - narcotics, or hormone medications

Responses to these questions were combined in a variety of models to calculate a breast pain severity score (BPSS) capable of distinguishing those patients most likely to require intervention for their pain from those requiring reassurance only. Sensitivity, specificity and positive predictive value were calculated for each of 13 models and a receiver operator characteristics curve was plotted to identify the appropriate break point in the best model.

Internal consistency was monitored using five question repeats. Questionnaires exhibiting more than one discrepancy were excluded.

Case Subjects

Eleven military clinics enrolled 1,340 patients receiving long-acting progesterones for contraception. Nine patient receiving Norplant® were excluded as were 11 patients who received Depo-Provera® for indications other than contraception. Questionnaires were
mailed to the remaining 1,320 patients; 26 were returned “undeliverable” and 671 were returned completed giving a response rate of 51.9% (number of completed questionnaires divided by the number of women actually receiving a questionnaire). Two of these patients had received 200 mg. of Depo-Provera® while the remainder had received 150 mg. Additional exclusions included age > 44 years (1), age < 18 years (6), medication not given (1), greater than 90 days elapsing from the time of administration of the medication (33), use of other hormonal agents in the preceding 12 months (110, of which 101 had received oral contraceptives), history of bilateral oophorectomy or unable to ascertain this history (5), pregnancy within the preceding six months (116), lactation within the preceding six months (48), and history of breast surgery within the preceding 30 days or unable to ascertain this history (4). None of the questionnaires exhibited more than one internal consistency discrepancy, but one was excluded because of insufficient data to measure internal consistency. After exclusions, 346 case-subject questionnaires remained for analysis.

<table>
<thead>
<tr>
<th>Depo-Provera® Subjects by Institution</th>
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<tbody>
<tr>
<td>Completed Surveys</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>309</td>
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<td>138</td>
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<tr>
<td>-Family Practice and OB/GYN</td>
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<td>43</td>
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<td>35</td>
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<td>11</td>
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<td>8</td>
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Control Subjects

Dates of birth of enrolled case subjects were forwarded from Tripler Army Medical Center in Honolulu, Hawaii to Michigan-based Vector Research via e-mail. Names and social security numbers of eight to 12 age-matched control subjects were then randomly selected for each case subject from a pool of all women eligible for health care in military medical treatment facilities in the United States. Current addresses were appended to this list from the DMIS database in Monterey, California. A total of 8,092 age-matched control subjects were obtained from DMIS. Of these, 1,418 had recognizable incomplete addresses. Questionnaires were mailed to 6,667 women; 1,291 were returned “undeliverable” and 1,433 were returned completed for a response rate of 26.7% (number
of completed questionnaires divided by the number of women actually receiving a questionnaire. Exclusion criteria included age greater than 44 years (2), history of bilateral oophorectomy or unable to ascertain this history (12), pregnancy within the preceding six months (191), pregnancy history not provided (4), lactation within the preceding six months (6), lactation history not provided (6), breast surgery within the preceding 30 days (8), use of unopposed estrogens (9), amenorrhea unexplained by hormonal medication usage (18) and menstrual history not provided (5). After exclusions, 1,150 control-subject questionnaires remained for analysis.

Statistical Analysis

Proportions were compared using Chi-square. Means were compared using two-tailed t-tests. Maximum likelihood estimates were calculated using logistic regression analysis. In the survey validation portion of the study certain examiner-derived information was compared with survey-derived information using the kappa statistic. Alpha error for each analysis was set at 0.05.

RESULTS

Survey Validation

Eighty-four women completing the survey were subsequently interviewed and examined by the P.I. These women ranged in age from 19 to 44 years with a median age of 32 years. Fifty-seven (67.9%) reported breast pain in the preceding 30 days. Eighty-one of the 84 women correctly reported their breast pain status for an accuracy of 96.4%. Two women without true breast pain reported pain: one had costochondritis and the second a small nodule which was slightly tender to palpation. One patient with classic cyclic mastalgia denied breast pain in the survey.

Three questions addressed the pattern of breast pain in relation to menstrual periods in an effort to distinguish cyclic from non-cyclic mastalgia. One point was scored for monthly or frequent breast pain, one for pain that was worst just prior to menstruation and one for pain that was relieved by the start of menstruation. As compared to the examiner's assessment of breast pain pattern, 0 points was never cyclic, one point was cyclic in 39% of cases, two points in 90% and three points in 100%. For the remainder of the study, surveys with two or more breast pain pattern points were designated “cyclic mastalgia”.

The survey contained several questions designed to distinguish chest wall pain from breast pain. Because only one respondent had chest wall pain it is not possible to
draw any correlations from these responses. It is apparent from this sample that primary chest wall pain is fairly uncommon in women reporting breast pain.

Breast pain severity was measured using a visual analog pain scale and six additional questions which addressed duration of pain, alterations in activity level and medication usage. Table one correlates the pain severity scores derived from the survey with those elicited by the examiner. In each instance, examiner-derived scores showed good correlation with survey-derived scores.

<table>
<thead>
<tr>
<th>TABLE 1: Measures of Breast Pain Severity: Correlation of Examiner-Derived Scores with Survey-Derived Scores.</th>
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<tbody>
<tr>
<td>Kappa Statistics</td>
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<td></td>
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<tr>
<td>Identical Scores</td>
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<td>------------------</td>
</tr>
<tr>
<td>VAPS</td>
</tr>
<tr>
<td>Duration</td>
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<tr>
<td>Activity</td>
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<tr>
<td>Medication</td>
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</tbody>
</table>

In this sample, 44.2% of patients with breast pain had mild pain appropriately treated by reassurance alone while 55.8% had more severe pain that would reasonably prompt consideration of medical intervention. Only one patient had pain severe enough to require hormonal intervention. Measures of breast pain severity from the four categories described above were combined in a variety of mathematical models to derive a Breast Pain Severity Score (BPSS) capable of distinguishing patients with mild pain from those with moderate or severe pain (i.e. pain likely to require intervention). The model with the most favorable characteristics on a plot of Sensitivity vs. 1-Specificity was VAPS Score X Duration Score. A BPSS greater than 10 derived from this formula had a sensitivity of 73.9%, a specificity of 87.5% and a positive predictive value of 89.5% for identifying patients likely to require intervention for their pain.

Accuracy of reporting was calculated for a variety of confounding variables by comparing survey-derived responses with examiner-derived responses. Results are reported as proportion of questionnaires in agreement with the examiner. These results, as well as the breast pain pattern and BPSS results, are summarized in Table 2.
TABLE 2: Proportion of Questionnaires in Agreement with Examiner-Derived Responses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Breast Pain</td>
<td>0.964</td>
</tr>
<tr>
<td>Moderate or Severe Pain (BPSS &gt;10)</td>
<td>0.795</td>
</tr>
<tr>
<td>Cyclic Pain</td>
<td>0.900</td>
</tr>
<tr>
<td>Hormonal Medication Use</td>
<td>0.964</td>
</tr>
<tr>
<td>Pregnancy (within 6 months)</td>
<td>1.000</td>
</tr>
<tr>
<td>Lactation (within 6 months)</td>
<td>1.000</td>
</tr>
<tr>
<td>Menstruation</td>
<td>0.982</td>
</tr>
<tr>
<td>History of Bilateral Oophorectomy</td>
<td>0.964</td>
</tr>
<tr>
<td>Menopausal Status*</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*derived from menstrual history in conjunction with hormonal medication usage and history of oophorectomy

Cross Sectional Study

After exclusions, 346 women receiving parenteral progesterones for contraception were compared with 1,150 randomly selected age-matched control subjects. Ages in both groups ranged from 18 to 44 years with a mean of 25.7 years in the Depo-Provera® group and 26.8 years in the control group (Figure 1).

Figure 1: Age Distribution

![Age Distribution Chart]
The study design ensured that subjects in the Depo-Provera® group had not used other hormonal contraceptives in the 12 months preceding the survey. The control subjects, on the other hand, had used a variety of hormonal agents in the year preceding the survey as outlined in Table 3.

<table>
<thead>
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<th>Table 3: Hormonal Contraceptive Use in the Control Group</th>
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<tr>
<td></td>
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<tr>
<td>Oral Contraceptives Only (OCP)</td>
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<tr>
<td>Depo-Provera Only</td>
</tr>
<tr>
<td>OCP and Depo-Provera</td>
</tr>
<tr>
<td>Norplant Only</td>
</tr>
<tr>
<td>OCP and Norplant</td>
</tr>
<tr>
<td>Depo-Provera and Norplant</td>
</tr>
</tbody>
</table>

Breast Pain Prevalence

The odds ratio (O.R.) for monthly or frequent breast pain for women using Depo-Provera® was 0.220 (95% C.I. = 0.152 - 0.318, P = 0.0001). Overall, 9.3% of women in the Depo-Provera® group reported frequent breast pain as compared to 20.8% of control subjects (P < 0.001). Similarly, 19.1% of Depo-Provera® patients reported breast pain in the 30 days preceding the survey as compared to 35.3% of control subjects (P < 0.001).

Among control subjects, the proportion of women reporting frequent breast pain increased with increasing age, ranging from 14.1% in the 18 to 21 year group to 28.6% in the 37 to 44 year group (P < 0.05). A similar trend was observed in the Depo-Provera® subjects; however, the reduction in breast pain prevalence was sustained across all age groups (Figure 2). This reduction in breast pain prevalence remained significant after correcting for the slight difference in mean ages between the two groups (O.R. 0.228, 95% C.I. = 0.157 - 0.329, P < 0.0001).
Figure 2: Prevalence of Mastalgia

Thin women (height:weight ratio > 3 cm/kg) had a lower prevalence of mastalgia than heavy set women (height:weight ratio < 2 cm/kg; 18.2% vs. 25.0%, P = 0.15, Figure 3). As a group, the Depo-Provera® subjects were slightly heavier than the control subjects (mean height:weight ratio 2.57 vs 2.65, P = 0.0002). Correcting for this minor difference in body habitus did not alter the prevalence results (O.R. with Depo-Provera® = 0.218, 95% C.I. = 0.150 - 0.315, P = 0.0001).

Figure 3: Mastalgia Prevalence by Body Habitus
Breast Pain Pattern

Breast pain was cyclic in 67.7% of control subjects with pain as compared to 21.2% of Depo-Provera® subjects (P < 0.001). As is common with cyclic mastalgia, the pain involved the entire breast in 50.1% of control patients but only 39.4% of Depo-Provera® patients. Stated conversely, mastalgia in Depo-Provera® subjects was most commonly non-cyclic (78.8%) and usually involved only a portion of the breast (59.9%; P < 0.01).

Breast Pain Severity

The prevalence of moderate - severe breast pain, (i.e. pain likely to require some form of treatment) was 2.3% in the Depo-Provera® group as compared to 4.9% in the control group (P < 0.02). Among those in the Depo-Provera® group who continued to have breast pain, however, the severity of the pain was similar to that in the control group. The mean BPSS in the Depo-Provera® group was 6.88 as compared to 6.42 for the control group (P = 0.50).

Medical Treatment

5.2% of Depo-Provera® subjects reported taking medication for breast pain, as compared to 8.9% of control subjects (P < 0.05). Acetaminophen and over-the-counter ibuprofen were the most common medications in both groups. One patient in the Depo-Provera® group and seven in the control group reported taking narcotics for breast pain relief. Hormonal agents were prescribed for breast pain relief in two of the control group patients, but none of the Depo-Provera® patients.

4.3% of the Depo-Provera® subjects sought medical advice for breast pain as compared to 7.0% of the control subjects (P < 0.05). Only 62.5% of the Depo-Provera® subjects and 51.8% of the control subjects with moderate - severe pain (BPSS > 10) received medical evaluation for their pain.

Interference with Activities

5.2% of Depo-Provera® subjects reported altering their usual activities because of breast pain as compared to 8.3% of the control group (P < 0.10). A similar proportion of Depo-Provera® and control subjects reported missing one or more days of work in the preceding 30 days because of breast pain (0.9% in each group).
Sub-Groups

Duration of Continuous Depo-Provera® Use

Of the 346 Depo-Provera® subjects, 36 (10.4%) were receiving the medication for the first time, 24 (7.0%) had been using Depo-Provera® for 3 months, 57 (16.5%) for 6 months, 74 (21.4%) for 9 months and 146 (42.3%) for 12 months or longer. Duration of continuous use was not known for one patient. The prevalence of mastalgia was inversely correlated with the duration of continuous Depo-Provera® use (R-squared = 0.835, P = 0.03, Figure 4). The prevalence of mastalgia in these patients ranged from 13.6% in the first time users to 8.2% in those who had been using the medication for 12 months or longer.

Figure 4: Prevalence of Mastalgia by Duration of Depo-Provera Use

Menstrual Periods

Sixty-five percent of women taking Depo-Provera® reported suppression of their normal menstrual periods. The prevalence and pattern of breast pain in these women was similar to that in women who continued to menstruate while on Depo-Provera®, however mean BPSS's were slightly higher in the amenorrheic sub-group (7.73 vs. 5.40, P =
0.28). Suprisingly, the amenorrheic sub-group reported a higher body mass than the menstruating sub-group (66.1 kg. vs. 62.6 kg, P = 0.02).

*Depo-Provera® Use in the Control Group*

128 control subjects reported receiving Depo-Provera® at least once during the 12 month period preceding the survey. The prevalence of monthly breast pain was 9.3% among the Depo-Provera® users as compared to 20.5% among the 391 subjects who had not used any hormonal contraceptives during this same period (P < 0.01). Of those control subjects with breast pain who had been exposed to Depo-Provera®, the pain was usually non-cyclic (59.5%) and typically only affected a part of the breast rather than the entire breast (58.3%). In contrast, breast pain in control subjects not using any hormonal contraceptives tended to be cyclic (76.7%, P < 0.001) and usually affected the entire breast (52.2%, P = NS).

**Attitudes Concerning Medical Treatment**

Attitudes concerning medical evaluation and treatment were culled from 2,104 evaluable surveys. Of these, 144 women (6.8%) had sought the advice of a health care provider specifically for breast pain. 51.4% reported being satisfied or very satisfied with the care they had received, while 18.8% reported being very dissatisfied (Figure 5). Of the 52 dissatisfied or very dissatisfied patients, 78.8% felt their health care provider lacked sufficient knowledge to effectively treat their breast pain, while only 55.8% cited a lack of sensitivity or compassion on the part of their provider (P < 0.02).
Military Readiness

Of 404 active duty service women in the control group who had experienced some breast pain in the 30 days preceding the survey, 12 (3.0%) reported that this pain had interfered with their ability to fire a weapon, 32 (7.9%) felt that it had interfered with their use of load bearing equipment, 97 (24.1%) felt it had interfered with physical training and 5 (1.2%) reported that they had been undeployable because of the pain. At any given time, mastalgia potentially disrupts the physical training activities of 5,000 - 14,000 active duty Army service women between the ages of 18 and 44 years, and may affect the deployability of 250 - 700 of these women.

DISCUSSION

Double-blind randomized prospective trials are the preferred approach for measuring the effectiveness of new medications, particularly for conditions as subjective as pain. Because progesterones are relied upon for contraception and produce amenorrhea in the majority of patients, they are not suitable for placebo-controlled trials in premenopausal women. For this reason we chose a cross-sectional design to compare the prevalence of mastalgia in a large group of women taking parenteral progesterones with that of an age-matched control group. This approach is particularly well suited to the military setting.
where the DMIS databases can be used to randomly select large numbers of controls, matched to a study population for any one of a number of demographic variables.

Though 30% of women presenting to surgical breast clinics present with a complaint of breast pain\(^1\), up to 68% will report breast pain when specifically asked about this symptom. Approximately half of these experience pain severe enough to warrant intervention. This high prevalence of mastalgia in the surgical breast clinic does not reflect that of the general population. In the current study, 35% of women report recent breast pain, but only 5% had pain likely to require intervention. Since our study population had a median age of only 26 years and mastalgia prevalence increases with increasing age, this figure would be higher for the population of premenopausal women as a whole. In addition, because this prevalence figure applies to all premenopausal women, the absolute number of women affected by this condition is quite large.

One proposed etiology of mastalgia is progesterone insufficiency associated with failure of maturation of the corpus luteum following an anovulatory cycle. Since the incidence of anovulatory cycles increases with increasing age, one would anticipate that the prevalence of mastalgia would also increases with increasing age. This was, in fact, observed in our population where the prevalence of frequent breast pain increased 0.7% per year between the ages of 18 and 44.

A consistent reduction in the prevalence of mastalgia was observed in subjects using Depo-Provera\(^\circ\) relative to an age-matched control group. This difference was highly significant across all age groups examined. Of concern in the analysis of this data was the discrepancy in questionnaire return rates between the Depo-Provera\(^\circ\) group and the control subjects. While 51.9% of Depo-Provera\(^\circ\) patients who received a survey form returned it, only 26.8% of the control subjects returned theirs. It would be reasonable to hypothesize that control subjects who experienced frequent breast pain would be more likely to complete a questionnaire that asked about breast pain, thereby artificially increasing the observed prevalence of mastalgia in this group. Two separate sub-group analyses were undertaken to address this possibility. First, since 128 control subjects reported using Depo-Provera\(^\circ\) at some time during the 12 months preceding the survey, it was possible to determine the prevalence and characteristics of mastalgia in these patients. Compared to the control subjects who had not used any hormonal contraceptives in the preceding 12 months, the control subjects using any Depo-Provera\(^\circ\) had a significantly lower prevalence of mastalgia and a non-cyclic pattern, affecting only a part of the breast that was consistent with that described for the case subjects currently using Depo-Provera\(^\circ\). Secondly, the prevalence of mastalgia in the case subjects decreased with increased duration of Depo-Provera\(^\circ\) use. While not a true dose:effect analysis this observation lends considerable
credence to the conclusion that Depo-Provera® use lowers the prevalence of mastalgia. The consistency of reduction in mastalgia prevalence observed in the cross sectional study combined with the results of these two sub-group analyses make it unlikely that this effect was caused by sampling bias.

Breast pain has been quantitated in the literature using a variety of methods ranging from simple binary scales (pain or no pain) to visual analog pain scales. A major thrust of the validation portion of this study was the construction of a BPSS that satisfied two important criteria: 1) calculable from a survey instrument, and 2) capable of distinguishing mild pain (minimal life style impact) from pain severe enough to prompt consideration of medical intervention. Four measures of pain severity were examined: intensity, duration, medication use and interference with usual activities. The product of the intensity and duration measures provided a BPSS with an accuracy of 79.5% for distinguishing mild breast pain (minimal life style impact) from breast pain severe enough to prompt consideration of medical intervention. Combining additional measures such as medication use or interference with usual activities resulted in less predictive BPSS’s as these variables were found to relate more to an individual’s response to pain than to the severity of the pain itself. For instance, one subject with breast pain rated as “mild” by the examiner reported regular use of narcotic pain relievers because she saw no reason to ever be in any pain at all, while others, with pain rated as “moderate” or “severe” stoically went about their usual activities without resorting to medications of any kind.

Premenopausal women as a group constitute a very heterogeneous population. Pregnancy, lactation, hormonal contraceptive use and ovarian dysfunction combine to confound any study that attempts to isolate the effects of any single hormonal intervention. The validity of any study which fails to account for these differences is in question. A large proportion of women returning completed questionnaires in both the Depo-Provera® and control groups were excluded from analysis (48.4% and 19.7% respectively). This difference in exclusion rates is primarily due to exclusion of women from the Depo-Provera® group who had used other hormonal contraceptives in the 12 months preceding the survey. This exclusion eliminates an important confounding variable and simplifies the interpretation of the reduction in mastalgia prevalence observed with Depo-Provera®. The vast majority of additional exclusions, in both groups, is accounted for by women who had been pregnant or lactating in the six months preceding the survey.

Only a small proportion of premenopausal women suffer from breast pain severe enough to warrant consideration of intervention, and in the majority of these, conservative measures, such as improved mechanical support for the breasts or non-steroidal anti-inflammatory agents is all that is required. In a small proportion, however, the pain
severely compromises a normal life style and hormonal agents may be required. Danazol, a modified androgen, is very effective at suppressing cyclic mastalgia but it is teratogenic and many women find its virilizing side-effects intolerable. Likewise, Tamoxifen, an estrogen agonist-antagonist, effectively palliates mastalgia but it has been associated with endometrial carcinoma and relapse is common following termination of a short course of therapy. Medroxyprogesterone acetate, the active component of Depo-Provera® has been evaluated for the treatment of mastalgia in one randomized prospective trial. This trial included only 18 patients, did not address issues of medication compliance and found no benefit. Our study evaluated women taking Depo-Provera®, a long-acting form of medroxyprogesterone acetate that is administered enterally. This approach guarantees compliance and any irregularities in timing of the medication or absorption are eliminated. The reduction in mastalgia prevalence observed with Depo-Provera® was striking and highly significant. Mastalgia patients treated with Depo-Provera® do not have to take medication every day and do not have to use the less effective barrier methods of contraception while on the medication. Depo-Provera® should be recommended to premenopausal women with mastalgia.

CONCLUSIONS

- The prevalence of mastalgia increases with increasing age, ranging from 14.1% in the 18 to 21 year group to 28.6% in the 37 to 44 year group.
- Mastalgia severe enough to prompt consideration of medical intervention affects more than 5% of all premenopausal women.
- Depo-Provera® use is associated with a significant reduction in the prevalence of mastalgia (odds ratio 0.220).
- Most patients with mastalgia are satisfied with the care they have received for this condition in the military medical system; most of those that are dissatisfied feel their health care provider lacks sufficient knowledge to deal with this condition.
- Mastalgia interferes with the physical training programs of 5,000 - 14,000 active duty Army servicewomen at any given time and may affect the deployability of 250 - 700 women.
- Depo-Provera® should be recommended to premenopausal women with mastalgia.
REFERENCES