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PRINCIPAL INVESTIGATOR: David M. Euhus, MD, MAJ, MC

CONTRACTING ORGANIZATION: Tripler Army Medical Center
Tripler Army Medical Center, Hawaii
96859-5000

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David M. E. ... May 95
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INTRODUCTION

Approximately 30% of women presenting to surgical breast clinics present for symptoms of breast pain¹. While approximately 85% of these women are adequately managed by reassurance after a thorough evaluation, 15% will find that the breast pain poses intolerable life-style limitations². Therapies for intractable mastodynia 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 results.

As a group, patients with benign breast disease have higher estrogen/progesterone ratios in their sera than women without symptoms of breast disease³. While this alteration is sometimes the result of an absolute estrogen excess^{4,5}, it more frequently represents diminished progesterone levels (so called "luteal insufficiency")^{6,7,8}.

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 mastodynia^{9,10}. 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

mastodynia¹¹. 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 group¹². The promegestone group experience a similar improvement rate. The only placebo-controlled trial of this drug, however, included 160 patients and recorded an 82.1% symptomatic improvement rate in the treatment arm as compared to 36.8% in the placebo arm¹³.

A variety of progesterone medications have been evaluated for the treatment of mastodynia. Among these is a progesterone ointment which was popularized in France. While an uncontrolled trial demonstrated improvement in 87% of 52 patients¹⁴, a double-blind, placebo-controlled, cross-over trial involving 25 patients failed to document any effect¹⁵. 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 ($P < 0.01$)¹⁶.

The most commonly prescribed progestagenic medication in the United States is medroxyprogesterone acetate (Provera[®]). This agent was assessed in a small ($N = 18$ evaluable patients) randomized prospective trial and found to be ineffective for mastodynia when administered in a dose of 10 mg per day on days 10 - 26 of the menstrual cycle¹⁷.

The literature describing progesterone supplementation for the treatment of mastodynia 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 progestones for the treatment of mastodynia 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 will be compared with those of an age-matched control population. When completed, this cross-sectional study will: 1) provide evidence for or against a role for progestones in the treatment and prevention of mastodynia, 2) estimate the impact of mastodynia 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 mastodynia patients.

METHODS

General Study Design

Women between the ages of 18 and 44 years, receiving Depo-Provera[®] injections for contraception, were enrolled at 11 OB/GYN or Family Medicine clinics evenly distributed across the United States. An informed consent form 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.

Questionnaire Design and Validation

The questionnaire was designed to record and quantify recent episodes of breast pain. A breast pain severity score is calculated based on intensity of the pain (visual analog scale), duration of the pain, disruption of activities of daily living and requirement for medication. The questionnaire distinguishes cyclic from non-cyclic mastodynia and queries satisfaction with medical evaluation and treatment. 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.

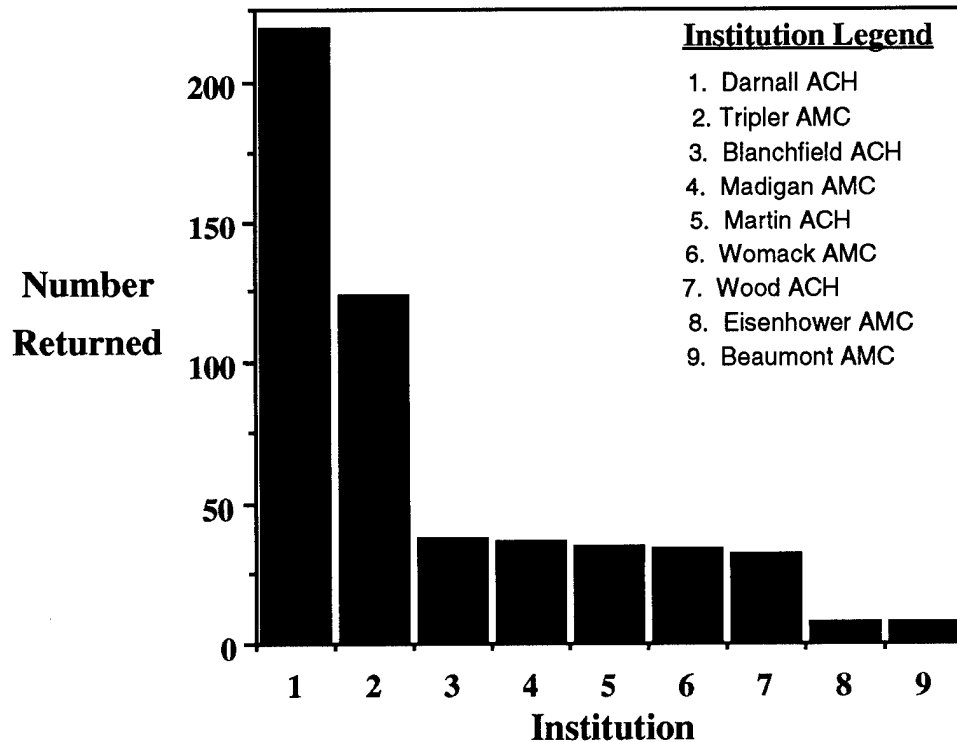
The questionnaire was developed and refined in the breast clinic at Tripler Army Medical Center. At the time of this writing the questionnaire, in its final form, has been administered to 68 women in this clinic who have subsequently been interviewed and examined by the P.I. The calculation of the breast pain severity score continues to undergo some refinement.

RESULTS

Analysis of survey data for the treatment and control groups awaits completion of accrual. Health care providers in a total of 15 clinics had initially expressed interest in participating in the study, but the rigors of the human use review process eliminated four of these. At the time of this writing, the survey has been formatted for automated reading on

a Scantron 8200[®] optical mark reader, and databases have been developed using Excel and SAS. The survey instrument has been approved by the Army Personnel Survey Office, nine institutional human use committees and the Office of the Surgeon General. Eleven OB/GYN or Family Medicine clinics across the United States are actively accruing Depo-Provera[®] patients. Treatment arm enrollment has reached 1,300 and, thus far, 533 volunteers have returned completed questionnaires for a return rate of 41%. A breakdown of completed questionnaires returned by institution is provided in figure 1. Control arm accrual is currently underway. At the time of this writing questionnaires have been mailed to 3,449 age-matched control subjects.

**Figure 1:
Completed Questionnaires by Institution**



CONCLUSIONS

Detailed analysis of the data currently being collected will provide important information about the prevalence of cyclic and non-cyclic mastodynia and will either support or refute a role for progesterones in the treatment of this condition.

Thus far this project has demonstrated a unique cooperation between medical specialties (general surgery, gynecology and family medicine) and between widely separated medical treatment facilities. The problems of age-matching and selection of a randomized control population have been addressed and the logistics of rapid transfer of large blocks of data have been simplified.

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