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Hormonal breast augmentation: prognostic relevance of insulin-like growth factor-I

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ABSTRACT

Many women would like to alter their breasts but are deterred by the risks involved. Silicone breast implants have been linked to a variety of illnesses, the most controversial of which are connective-tissue diseases. These circumstances urged us to perform this pilot study using a non-invasive method that involved the application of 17β-estradiol as it is known that estradiol enhances expression of insulin-like growth factor-I (IGF-I) which can promote growth in breast tissue.

Forty-five women were included in the study. Their breast volume, IGF-I, prolactin (PRL) and estradiol levels were measured before treatment and between each application of 80 mg estradiol polyphosphate. The women's satisfaction with the results obtained was also subsequently evaluated.

In 21 women (46.7%), breast size increased from 824.3 ± 13.7 mm to 898.5 ± 12.5 mm after 6 months. In these women a significant increase in IGF-I values was noted after 4 weeks of treatment. The increase in IGF-I values was not statistically significant in the remaining women. In addition, treatment was not successful in these women.

IGF-I concentration seems to be of prognostic value as far as the response of breast tissue to estrogen stimulation is concerned. If IGF-I levels do not increase within 1 month, treatment should be discontinued. If IGF-I values do increase, this indicates that treatment is likely to be successful and can therefore be continued.

INTRODUCTION

Throughout human history until the present day, the female breast has been a symbol of sexuality and fertility[1]. With respect to Western cultures, it may be stated that the emphasis on the female breast has never been greater than during the last 20 years, as evidenced by the creations of garment designers as well as by the film and advertising industries.

This sociocultural emphasis combined with the perfection of alloplastic implants, which make it possible to achieve almost perfect results, has led to an ever-increasing demand for augmentation mammaplasty among women. Mammaplasty may consist of artificial enlargement, correction of shape or greater firmness. Augmentation mammaplasty is currently one of the most frequently performed cosmetic operations[2].

Although good cosmetic results can be swiftly achieved by inserting alloplastic silicone expanders, these procedures are associated with specific disadvantages, namely with the risk of surgery and

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anesthesia, risk of infection[3] and various immunological complications caused by silicone implants[4].

These factors, together with the fact that a large number of women visited our Department of Endocrinology between 1991 and 1993 with the desire to undergo non-invasive treatment for breast augmentation, urged us to perform this study.

We used a non-invasive method to augment the breast or to increase firmness of tissue. Among the studies published in the German literature, there are only two instances of hormonal breast augmentation[5,6], whereas not a single instance has been reported in the English literature.

The aim of this study was to determine the efficacy of hormonal breast augmentation by (1) measuring the size of the breast during the application of hormones; (2) assessing the women's satisfaction with the results of augmentation; and (3) measuring estradiol, insulin-like growth factor-I (IGF-I) and prolactin (PRL) serum levels during hormonal treatment.

MATERIALS AND METHODS

Patients

A total of 45 premenopausal nulliparous women (mean age 27.9 ± 4.25 years, mean body mass index (BMI) 23.98 ± 3.41 kg/m^2) with regular menstrual cycles who had come to our department for hormonal breast augmentation underwent the treatment for the entire period of the study. The women underwent a basic mammography to exclude pathological mammary changes and a gynecological examination. After these examinations and after the exclusion of possible contraindications, all participants underwent 6 months of treatment with 80 mg estradiol polyphosphate (Estradurin®, Kabi Pharmacia, Uppsala, Sweden) applied intramuscularly at intervals of 10–12 days and with progestagen suppositories (each suppository containing 0.4 g of progesterone) from the 15th to the 24th day of the menstrual cycle. Estradiol, PRL and IGF-I values were evaluated at intervals of 4 weeks, i.e. shortly before every third application of estradiol. At this time, the size of the breast was measured and the patient's degree of satisfaction was obtained on a self-rating score consisting of the following ratings: completely satisfied, very satisfied, satisfied, dissatisfied, completely dissatisfied. A mammography and the gynecological examination were repeated after 6 months.

Hematological assessment

All analyses for each individual subject were performed in a single assay and in duplicate. Serum IGF-I levels were measured by radioimmunoassay (Serono SERIA®, Geneva, Switzerland) with an intra-assay coefficient of variation (CV) of 6.2% and an interassay CV of 10.3% at 0.5 IU/ml. Plasma was assayed for estradiol by radioimmunoassay kits obtained from Serono Diagnostics. The lower limit of sensitivity of the assay was 1.5 pg/ml. Serum PRL levels were determined by ENZYMUN® immunoassays on an ES600 automatic analyzer (Boehringer Mannheim, Germany).

Data analysis

The statistical evaluation was performed using Schubö and Uehlinger's version of the SPSSx program[7]. Initially, mean values (x) and standard deviations (SD) of breast size as well as serum levels of IGF-I, estradiol and PRL were determined. Thereafter, group differences were examined for statistical significance using Student's *t*-test. As regards the volunteers' degree of subjective satisfaction, absolute and relative frequencies were determined and median values as well as standard deviations were obtained.

RESULTS

Changes in breast size

In 21 women (group 1, mean age 28.29 ± 3.98 years, mean BMI 22.87 ± 3.65 kg/m^2), breast size increased from 824.3 ± 13.7 mm to 898.5 ± 12.5 mm after 6 months of treatment ($p < 0.01$). In 24 women (group 2, mean age 27.54 ± 4.52 years, mean BMI 23.85 ± 3.18 kg/m^2), breast size did not increase significantly (Figure 1).

Patient satisfaction

Thirteen women whose breast size increased significantly were completely or very satisfied with the results of treatment at the end of the study. Even in the group of women whose breast size did not increase, six were completely or very satisfied

with the treatment. Two women from the successful group and four from the unsuccessful group were completely dissatisfied with the treatment (Table 1).

Mammographic changes

During treatment with estradiol polyphosphate, no woman showed any mammographic changes.

Changes in hormonal parameters

During estradiol polyphosphate treatment, estradiol values increased from 45.1 ± 5.9 pg/ml to 161.1 ± 17.7 pg/ml and did not differ between the two groups (Figure 2). Moreover, PRL values increased in both groups. Here too, no difference was observed between the two groups (Figure 2). IGF-I values revealed a greater extent of variance. Even after one month of treatment, IGF-I values increased from 1.22 ± 0.31 mIU/ml to 1.42 ± 0.71 mIU/ml in the 21 women whose breast size increased significantly by the end of the study. In the remaining 24 women, IGF-I levels in the serum did not change during the 6 months of treatment (Figure 2).

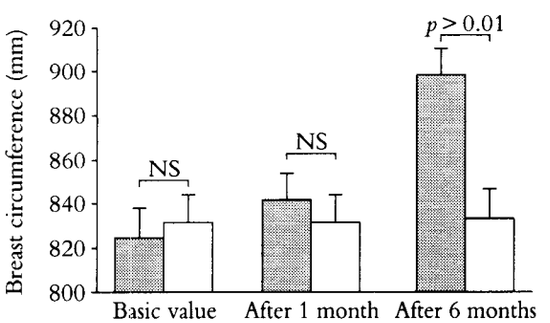

Figure 1 Change in breast size (mm ± SD) in women with (group 1, $n = 21$) and without (group 2, $n = 24$) measurable increase in breast size. Shaded bars, group 1; open bars, group 2; NS, not significant

DISCUSSION

Augmentation mammaplasty (without reconstructive surgery after mastectomy due to malignancy) is the second most frequently performed cosmetic

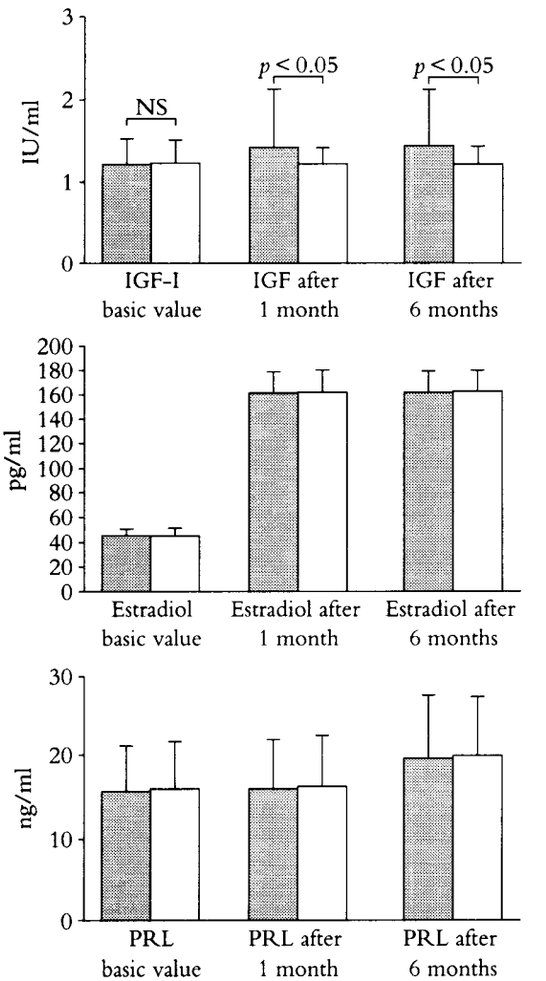

Figure 2 Changes in hormonal parameters of women with (group 1) and without (group 2) breast size increase during course of treatment with 80 mg of estradiol polyphosphate. Shaded bars, group 1; open bars, group 2; IGF, insulin-like growth factor; PRL, prolactin

Table 1 Subjective satisfaction at the end of treatment. Comparison of women with (group 1, $n = 21$) and without (group 2, $n = 24$) measurable increase in breast size and surgical methods (see reference 8)

Degree of satisfaction	*Group 1* (%)	*Group 2* (%)	*Surgical augmentation* (%)
Completely satisfied	19.0	8.3	64.0
Very satisfied	47.6	16.7	22.0
Satisfied	14.4	33.3	9.0
Dissatisfied	9.5	24.9	4.0
Completely dissatisfied	9.5	16.8	0.0

procedure after suction-assisted lipectomy[2]. Notwithstanding the great progress made in this field, surgical breast augmentation for purely cosmetic reasons is still associated with surgical and anesthesiological risks as well as with postoperative complications such as wound infection[3], scar tissue contraction[8], difficulty during subsequent lactation[9], increased risk of mammary carcinomas as well as the difficulty of detecting them[10,11]. Autoimmune diseases occasionally caused by silicone implants[12] led the US Federal Drug Administration to ban silicone implants[4].

Gabriel and co-workers[13] showed in their recent report that after initial breast implantation complications occur in 27.8% of cases which make a further surgical procedure necessary[13]. A major advantage of our approach to breast augmentation is that it led to no further complications.

After 6 months of treatment, breast size significantly increased in 46.7% of our patients. While 44.4% were very satisfied or completely satisfied with the treatment, 24.4% were satisfied and only 31.3% were dissatisfied or disappointed.

The divergence between objective increase in breast size and the number of women who were satisfied with the treatment may be attributed to the fact that the patients' expectations differed widely. This divergence was definitely not related to a quantitative increase in breast size only. Rather, additional factors such as improved shape of the breast, increased firmness as well as psychic factors played an important role.

In 1994, Young and associates[8] examined the satisfaction of 112 patients after augmentation mammaplasty. Their study revealed that 86% of the patients were satisfied with the results of the treatment (Table 1). However, this high degree of satisfaction was obtained at the expense of a 21% complication rate (capsular contracture, hematoma and loss of sensation in the nipples).

The hormonal control of growth and differentiation of the mammary gland has been the subject of intense investigation. In addition to various hormones, growth factors are important regulators of mammary development. Receptors for IGF-I and IGF-II have been found in both normal mammary tissue[14] and in breast cancer cell lines[15]. Recent data show that a combination of estradiol and progesterone treatment produced a twofold increase in IGF-I receptor mRNA levels in normal breast tissue compared with untreated tissue[16].

In our patient collective, the IGF-I values are an interesting aspect. IGF-I values increased during Estradurin treatment in those women whose breast size increased after 4 weeks of treatment. Hence, an increase in IGF-I value is prognostically significant. If these levels increase during treatment, then treatment may be expected to be successful.

Since the IGF-I receptor is the mediator of the mitogenic response to IGF, its upregulation by estradiol is likely to have a biological significance in the normal breast[17]. Thus, the sensitivity of normal breast tissue to mitogenic stimulation by estradiol may be partly dependent on the circulating levels of IGF-I and on the upregulation of the IGF-I receptor in the epithelium of the mammary gland. Historically, IGF-I has been known as an endocrine factor produced in the liver under the control of growth hormone. Together with other hormones, estrogen is also known to be one of the regulators of IGF-I, enhancing its expression in certain estrogen-sensitive cells and tissues[18]. In 1994, Umayahara and colleagues[19] elucidated the molecular basis of IGF-I regulation by estrogen action. They reported that the IGF-I gene promotor is a target of estrogen regulation. Our results are consistent with the suggestion that estradiol may act as a stimulator of proliferation in normal human breast tissue involving IGF-I. But it must be clearly stated that IGF-I and IGF-II in combination with estradiol are synergistic in their effects on the growth of MCF-7 breast cancer cells in culture[20], and that the expression of the IGF-I receptor in MCF-7 breast cancer cells is increased by estradiol treatment[21]. After discontinuing hormone treatment, breast size may decrease to pretreatment size again, because of the decrease in the proliferation stimulus for the breast tissue. Lauritzen[6] recommends the use of oral contraceptives to maintain achieved breast size. But convincing data are missing. Grodstein and co-workers[22] showed in their recent study that the proportion of deaths due to breast cancer was higher in women with hormonal replacement therapy than in the general population, therefore, although successful in about 50% of the women, hormonal breast augmentation should not be recommended uncritically, and it should only be carried out after the patient has been given detailed information.

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