

## Prolactin and autoimmunity in silicone mammoplasty\*

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The article is devoted to the study of the effect of silicone as an adjuvant on the development of autoimmune complications of mammoplasty and the development of autoimmune syndrome induced by adjuvants “ASIA”. This controlled cohort prospective non-randomized research is based on analysis of clinical observations of 121 patients undergoing plastic surgery on the mammary glands for aesthetic purposes, as well for reconstructive and oncological indications, both with and without silicone implants. To obtain preliminary results and evaluate the study, 27 blood serum samples were randomly selected, in which the dynamics of prolactin levels and autoantibody profiles towards 7 common autoantigens were studied before and after 3 and 6 months post-surgery. It was found that 5 out of 27 patients after mammoplasty showed an increase in 2 types of autoantibodies (against modified citrullinated vimentin and annexin V). Patient in need for mammoplasty have increased serum levels of prolactin at the day of operation. After surgery on the mammary gland, the level of prolactin decreases to normal range within 3 months, even if it was significantly higher than normal before surgery. Both of these facts require additional research and analysis on a wider cohorts of patients.

**Keywords:** plastic surgery, breast augmentation, breast reconstruction, silicone, autoimmune diseases, autoantibodies, adjuvant, autoimmune inflammatory syndrome induced by adjuvants (ASIA).

### Relevance

In 2011, Y. Shoenfeld et al. coined a new nosological entity — autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA). One of the nosologies of this syndrome describes adjuvant breast disease [1; 2]. The study of this aspect is extremely important, as more than 20 million pairs of implants have been inserted in the world [3] and

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it seems necessary to verify the relationship of occurrence of autoimmune complications with previous silicone breast plastic surgery. Now it's not possible to reveal a certain correlation, because on the one hand, the number of publications about the development of systemic autoimmune diseases among women after silicone implantation is growing [4; 5], but on the other hand, many authors deny the connection between silicone mammoplasty and autoimmune disorders [6]. This study aims to clarify the links between silicone mammoplasty and some features of immunoendocrine status of its female recipients. The prolactin level was of special interest, because this bioregulator is a key controller of breast ontogenesis and function and also due to roles of prolactin as potent paracrine and endocrine stimulator of autoimmunity [7]. Several researchers, including ourselves, have described hyperprolactinemia and even galactorrhea cases after silicone mammoplasty [8].

## **Aim**

To study the levels of autoantibodies against 7 common autoantigens and prolactin concentrations in dynamics in blood sera of female patients before and at different terms after silicone mammoplasty. The research design is a controlled cohort prospective non-randomized study. It is based on the analysis of clinical observations of 121 patients undergoing plastic surgery on the mammary glands for aesthetic purposes, as well as for reconstructive and oncological indications, both with and without (control group) silicone implants. Patients were included in the study voluntarily, anonymously, signing an informed consent to participate in the study and consent to the storage of biological material in the Laboratory of the Mosaic of Autoimmunity, St. Petersburg State University.

Patients were included in the study having different initial statuses regarding silicone implants: some of them had no implants before the observation period, some had silicone implants for varied periods of time. One subgroup of patients had implants installed during the observation period, the other subgroup received implants after the initial installation of silicone-made tissue expander, followed by replacement with an implant. The third subgroup was replacing their previously installed implants. Control group of patients went through breast surgery without implants. In all of them serum prolactin level before and 3/6 months after surgery was measured by ELISA.

### **Autoantibodies studied:**

- Antibodies to modified citrullinated vimentin (MCV);
- IgG Cardiolipin antibodies;
- IgM Cardiolipin Antibodies;
- Antibodies to Hep-2 cell nuclear antigens;
- Antibodies to beta2-glycoprotein 1;
- Antibodies to thyroid peroxidase;
- Antibodies to thyrotropin receptor;
- Antibodies to thyroglobulin;
- IgG annexin V antibodies;
- IgM annexin V antibodies.

Checkpoints studied were: 0, 3, 6 months after surgery. Because of phenomenon of natural occurring physiological autoimmunity, only those samples with autoantibodies con-

centration above the upper limits of the normal ranges recommended by the producers of immunodiagnostic kits were considered to be “seropositive” for certain autoantibody.

To obtain preliminary results and evaluate the interim results of study, 27 blood sera samples were randomly selected, in which the dynamics of prolactin levels and autoantibody levels were studied before operation, and also after 3 and 6 months post-surgery.

Measurements were made by enzyme-linked immunosorbent assay (ELISA) in the Resource Center of the Development Molecular and Cellular Technologies of the Science Park of St. Petersburg State University and the Laboratory for the Diagnosis of Autoimmune Diseases at I. P. Pavlov First St. Petersburg State Medical University.

Statistical processing of the data was performed as follows.

Binary logistic regression with mixed effects and parameters estimation method were used by Christensen [9]. The dependent variable was the presence or absence of antibody titer, and the independent variable was sampling time. Individual variability was taken into account by introducing the random factor “patient” into the regression model. The Akaike’s information criterion was used to describe the results (Akaike’s ‘An Information Criterion’, AIC), the logarithm of maximum likelihood (log-likelihood, LR), the degrees of freedom (degrees of freedom, df), and the value of the model (p). To correct the significance level during multiple testing of the hypothesis, the Benyamini-Yekutieli correction was used. Changes were recognized as statistically significant at  $p < 0.05$ . Mathematical modelling was carried out in the R v3.6.0 programming language [10].

## Results

The results are presented below in tables and plots.

*Table 1. Dynamics of the proportion of autoantibodies-seropositive cases at the preoperative stage and at 3 and 6 months of post-surgery period in female recipients of silicone mamoplasty*

Antibodies to:	Baseline (n (%))	3 month (n (%))	6 month (n (%))	P
IgG annexin V	2 (7.4 %)	1 (3.7 %)	1 (3.7 %)	1.000
IgM annexin V	1 (3.7 %)	1 (3.7 %)	1 (3.7 %)	1.000
Modified Citrulline Vimentin (MCV)	0 (0.0 %)	0 (0.0 %)	2 (7.4 %)	<b>0.048</b>
IgG Cardiolipin	0 (0.0 %)	0 (0.0 %)	1 (3.7 %)	0.366
<b>IgM Cardiolipin</b>	0 (0.0 %)	1 (3.7 %)	3 (11.1 %)	<b>0.008</b>
Hep-2 Cell Antigens	0 (0.0 %)	0 (0.0 %)	1 (3.7 %)	0.366
Beta2-glycoprotein 1	3 (11.1 %)	3 (11.1 %)	3 (11.1 %)	1.000
Thyrotropin receptor	1 (3.7 %)	2 (7.4 %)	1 (3.7 %)	1.000
Thyroglobulin	2 (7.4 %)	2 (7.4 %)	2 (7.4 %)	1.000
Thyroid peroxidase	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	–

A statistically significant increase in percentage of seropositive cases was registered for two out of all checked types of autoantibodies: those against modified citrullinated

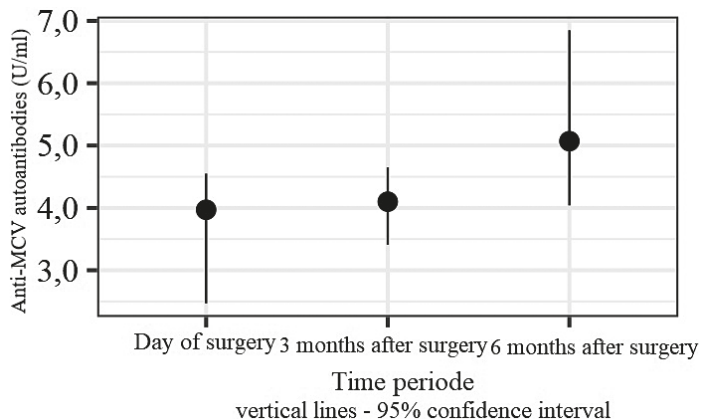


Fig. 1. The dynamics of anti-MCV autoantibodies serum level during 6 months of observation in female recipients of silicone mammoplasty. Vertical axis: anti-NCV serum concentration, U/ml; horizontal axis: left to right day of operation, 3 and 6 months after surgery. Points indicate mean and lines — standard errors of values)

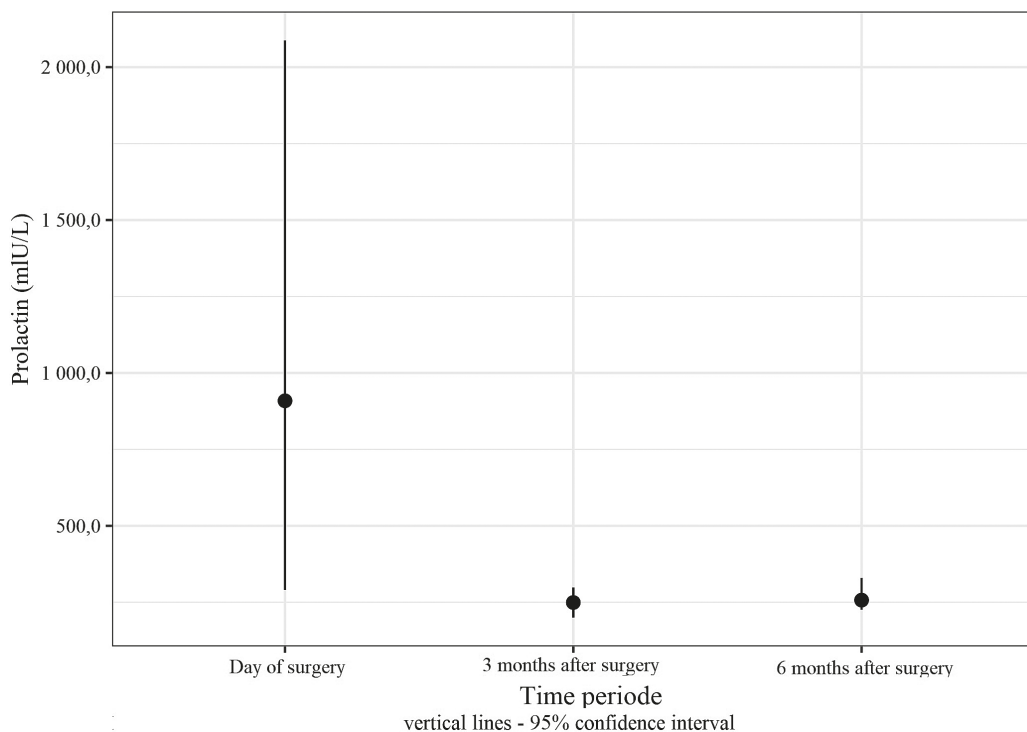


Fig. 2. The dynamics of prolactin serum level during 6 months of observation in female recipients of silicone mammoplasty. Vertical axis: prolactin serum concentration, mIU/ml; horizontal axis: left to right day of operation, 3 and 6 months after surgery. Points indicate mean and lines — standard errors of values)

vimentin and class IgM anti-cardiolipin autoantibodies. In the first case, two patients had an immune shift at 6 months. In the second case, three patients showed evidence of the shift at 6 months. Figure 1 illustrates the dynamics of anti-MCV sutoantibodies in silicone mammoplasty recipients.

The average blood prolactin level among patients on the day of mammoplasty was significantly elevated. Blood prolactin levels of the operated patients decreased in the postoperative period relative to the preoperative level down to normal range, stabilizing to 6 months after surgery (Table 2 and Figure 2). The cause of hyperprolactinemia in patients with aesthetic mammoplasty can be a psychogenic factor, as well as stress in connection with the procedures and breast examination prior to surgery. The existence of the phenomenon of psychogenic (stressogenous) hyperprolactinemia is well-known [11].

*Table 2. Prolactin level dynamics at the preoperative stage and at 3 and 6 months of post-surgery period in female recipients of silicone mammoplasty*

Indicator	Time	Md [Q1; Q3]
Prolactin	0 month	908.8 [249.0; 3004.8]
	3 month	246.4 [172.4; 414.0]
	6 month	246.4 [184.1; 350.1]

An *exception* were two patients with hyperprolactinemia and even galactorrhea developed in the early postoperative period after mammoplasty. Dopaminergic therapy was used to treat the condition, one of the cases described elsewhere [8].

## Conclusions based on the interim study

1. There is a change in the immune status in some patients after mammoplasty — an increase in levels of 2 types of autoantibodies.
2. The level of prolactin in female patients preparing for mammoplasty is increased. This presumably psychogenic hyperprolactinemia should be taken into account for its possible pro-autoimmune effect.
3. After surgery on the mammary gland, the level of prolactin decreases to normal range, even if it was significantly higher than normal before surgery.

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