Current status of silicone gel breast implants

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W Peters. Current status of silicone gel breast implants. Can J Plast Surg 1994;2(1):18-23. There are currently three main areas of concern regarding the safety of silicone gel implants: implant failure; a potential link to autoimmune connective tissue disease; and a possible link to breast cancer. All silicone gel implants 'bleed' small levels of silicone. In addition, silicone gel implants appear to fail (leak or rupture) with time. Most implants in place for less than seven years appear to be intact. It appears that many silicone gel implants implanted for over seven years are probably ruptured or leaking. Implant failure may occur simply from deterioration. Implants can also rupture following closed capsulotomy. Mammography and ultrasound studies are generally not helpful in predicting implant failure. Magnetic resonance imaging (MRI) studies appear to be useful, but the 'breast coil' necessary to perform these studies is not currently available in most MRI units in Canada. The significance of implant failure is not known. There is a growing (but unproven) concern that immunological sensitization to silicone could develop in women with silicone gel implants. An extensive review of all clinical and immunological studies in the current literature has failed to demonstrate any conclusive link between silicone gel implants (whether intact or nonintact) and the development of autoimmune connective tissue disease or other disease process. However, large scale epidemiological studies remain to be done. Several large studies have proven that there is no relationship between silicone gel implants and the development of breast cancer.

Key Words: *Breast carcinoma, Connective tissue disease, Rupture, Silicone gel breast implants*

Situation actuelle des prothèses mammaires au gel de silicone

RÉSUMÉ : Actuellement trois grandes questions se posent au sujet de la sécurité des prothèses au gel de silicone : soit la défaillance des prothèses, leur lien potentiel avec une maladie auto-immune du collagène et leur lien possible avec le cancer. Toutes les prothèses de silicone fuient à des degrés minimes. De plus, les prothèses au gel de silicone semblent présenter des faiblesses (fuites ou ruptures) avec le temps. La plupart des implants en place depuis moins de sept ans semblent intacts. Par contre, les prothèses posées depuis plus de sept ans risquent de fuir ou de se rompre. La défaillance des prothèses survient simplement des suites d'une détérioration ou les prothèses peuvent se rompre après une capsulotomie serrée. La mammographie et l'échographie ne sont en général pas utiles pour prévoir la défaillance des prothèses, contrairement à l'imagerie par résonance magnétique (IRM), quoique les dispositifs nécessaires à l'exécution de cette épreuve diagnostique ne soient pas encore disponibles dans la plupart des établissements où se pratique l'IRM au Canada. La portée de la défaillance des prothèses reste méconnue. On s'inquiète de plus en plus (quoique sans preuves) d'une sensibilisation immunologique au silicone, qui pourrait s'installer chez les porteuses de prothèses au gel de silicone. Une revue approfondie de tous les essais cliniques et immunologiques rapportés dans la littérature actuelle n'a pas réussi à établir un lien concluant entre les prothèses au gel de silicone (intactes ou non) et l'installation d'une maladie auto-immune du collagène ou d'autres processus pathologiques. Toutefois, il est nécessaire d'entreprendre de grandes études épidémiologiques. Plusieurs études d'envergure ont prouvé qu'il n'y a aucun lien entre les prothèses au gel de silicone et le cancer du sein.

Silicone gel breast implants were introduced clinically in 1962 at which time they did not require Food and Drug Administration (FDA) approval. In 1976, the United States Congress passed the Medical Device Amendments, giving the FDA power to regulate all medical devices (1,2). However, because they had already been in use for 14 years, silicone gel implants were deemed 'clinically safe', and thereby received grandfathered status, bypassing the pre-market approval process that currently governs new devices. In 1982, the Federal Registry divided medical devices into three classes: class I - located outside the body; class II - temporarily implanted; and class III - permanently implanted. Silicone gel implants were initially placed in class II. During the 1980s, breast augmentation surgery became the commonest aesthetic procedure performed by plastic surgeons in North

America. This surgery provided tremendous benefit to a huge number of women. Most implants were of the silicone gel type. Over one million patients have received these implants.

In 1991, silicone gel implants were moved from class II to class III. The FDA then asked all implant manufacturers to submit pre-market approval applications establishing their safety (2,3). These applications were reviewed by advisory panel hearings. In the fall of 1991, the FDA stated: "Immunological sensitization may be a serious risk associated with the implantation of silicone-gel-filled breast prostheses. Questions have been raised about the relationship between silicone and various connective tissue disorders, including scleroderma" (3). In January 1992, FDA Commissioner David Kessler called for a voluntary moratorium on the use of silicone gel breast implants, until the advisory panel could conduct further hearings (4). In the United States, the moratorium was lifted a month later for those patients undergoing breast reconstruction. Patients who were having cosmetic

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breast augmentation procedures, however, could receive silicone gel implants only if they enrolled in an extensive five-year 'adjuvant study'. This moratorium was also adopted in Canada, where it has remained in place for both reconstructive and cosmetic patients.

These announcements were followed by a period of considerable misinformation in the general media, particularly concerning anecdotal reports of connective tissue disease in some patients with silicone gel implants. This produced anxiety in patients and, in some cases, led to 'mass hysteria' about the safety of breast implants (5). In the United States, thousands of lawsuits have been initiated by breast implant patients against implant manufacturers. In Ontario, a class-action suit was launched in November 1993. Throughout Canada, numerous other lawsuits have now been initiated, all against the manufacturers of breast implants.

The alarm by patients concerning the safety of their implants has been reinforced more recently by further media developments. On December 5, 1993, Dow Corning announced a proposed world-wide and industry-wide \$4.75 billion (US) fund, that would "serve as an insurance policy for women with breast implants ... over the next 30 years". This proposed settlement was designed by lawyers representing plaintiffs and defendants, in thousands of US lawsuits, to assist patients if they do develop certain problems. Dow Corning - the largest manufacturer of silicone gel implants in the United States - expects that its share of this settlement will be \$1.24 billion. This settlement fund has been perceived by the public as a 'declaration of guilt' by the manufacturers of gel implants.

At this point in time, it is interesting to note that in its 1991 report (2), the FDA stated: "There is no conclusive evidence at present that women with breast implants have an increased risk of developing arthritis-like diseases or other autoimmune diseases.... In weighing the possible long-term risks of silicone breast implants, it is important to bear in mind - and this applies to any number of substances we encounter in everyday life - that not being able to completely rule out a risk does not necessarily mean there is one."

SILICON AND SILICONE

Silicon is the second most abundant element on the earth's surface and constitutes about 28% by weight (6). (Oxygen is the commonest element at 47%.) Silicon, however, is not found in its simplest form in nature. Rather, it most frequently occurs as a silica which is composed of silicon dioxide (SiO_2) (6). In humans, silicon is found in significant concentrations in hair, bones (particularly unclosed epiphyses), epidermis and dental enamel (6). Silicon is an essential component of glycosaminoglycans, a component of connective tissues (7).

Silicone is a generic name for a family of silicon-based polymers. Silicone is derived from a series of chemical reactions to produce a monomeric building block of dimethylsiloxane (Si-O backbone with methyl sidegroups). Antioxidants, accelerators, dyes and plasticizers are generally not used in the synthesis of medical grade silicone (7,8), whereas these compounds are employed in the synthesis of other grades of silicone.

Medical grade silicone can be processed into three different chemical forms: oils, gels and rubbers. Oils are made from linear chains of monomer and are used for coating needles and syringes, for lubricating surgical instruments and in the manufacture of gastrointestinal medications (7,8). Gels (lightly cross-linked branching polymers - the more branches the thicker the gel) are used as filler materials for breast and testicular implants. Rubbers (elastomers) (long chains of heavily cross-linked polymers joined by side branching) are used to make breast implant shells, to coat pacemakers and heart valves, and to make catheters, drains, eye lenses, hydrocephaly shunts and certain birth control devices (1,8). Silicone was initially chosen for use as an implantable device because of its 'biological inertness and stability' (9).

SAFETY OF SILICONE GEL IMPLANTS

There are currently three main areas of concern regarding the safety of silicone gel implants: implant failure or rupture; a potential relationship between silicone and autoimmune connective tissue disease; and a potential relationship between silicone and the development of breast carcinoma.

Implant failure

Since 1978, it has been recognized that a small amount of silicone can be expected to 'bleed' from all clinically intact implants (10,11). More recently, Dow Corning has reported annual 'bleed' rates of 60 to 100 mg for implants made before about 1982, and 5 to 10 mg for newer implants (12). The medical significance of this 'bleed' remains unknown.

In addition, implants may develop a leak or a frank rupture. Earlier studies by Peters (13) and Van Rappard and colleagues (14) suggested that the strength of implants decreased over time. More recently, studies by Peters and colleagues (15) and de Camara and co-workers (16) demonstrated a positive correlation between the duration of implantation time and the number of leaking or ruptured implants. In the study by Peters and coworkers, over 93% of implants which had been in place for five years or less remained intact. However, only 30% of implants which had been in place for six to 15 years remained intact. In the smaller study by de Camara's group, all implants older than 10 years were leaking or ruptured (15). The etiology of leakage and rupture remains to be fully elucidated. Implants may simply undergo a progressive deterioration with time. It is recognized that implants made during the past eight to 10 years are stronger than those made earlier.

Closed capsulotomy has been documented as a potential cause of implant rupture (10,12,17). In 1978, in a study of 50 surgeons, it was shown that the compression forces generated during closed capsulotomy ranged from a mean of 10.6 pounds per square inch (psi) to 15.2 psi, depending on the technique employed (18). In 1982, Peters showed that 'new' silicone gel implants ruptured with a mean compression force of 6.32 psi (range 4.9 to 9.9), and that explanted silicone gel implants ruptured with a mean compression force of 4.61 psi (range 0.6 to 9.8 psi) (13). A survey of 583 surgeons showed that 15.9% of 5579 implants which had undergone closed

capsulotomy were subsequently found to be ruptured at open capsulotomy (10). After these findings, implant companies began to add disclaimers advising against closed capsulotomy. In addition, they announced that implants were now being constructed so that they would be much stronger.

Of particular concern today is the difficulty in diagnosing 'bleeding', leaking or rupturing of silicone gel implants. Neither mammography (19) nor ultrasound techniques (20) appear to be very helpful in assisting with these diagnoses. Magnetic resonance imaging (MRI) techniques appear to be advantageous. In a study of 100 patients with silicone gel implants, Ahn and co-workers demonstrated implant ruptures with a sensitivity of 76% and specificity of 97%, with a 3.75% incidence of false-positive and false-negative results (21). However, appropriate MRI techniques are not currently available in most centres in Canada. In Toronto, for example, there are six MRI units, but none of these units is equipped with a 'breast coil' to assess properly breast implant integrity.

The significance of free silicone from 'bleeding', leakage or implant rupture remains unknown. Clinically, the majority of this silicone appears generally to be contained within the capsular tissue surrounding the implant. However, free silicone has been found in axillary lymph nodes and other tissues (22). There is currently no evidence that free silicone is associated with the development of any medical disease.

Connective tissue disease

Currently, there is a growing (but unproven) concern that immunological sensitization to silicone could develop in women with breast implants, and that this could lead to the development of connective tissue disease in certain susceptible patients (23). The initial reports of this potential relationship came from Japan, where, from 1950 until 1970, breast augmentation procedures were widespread and involved the direct injection of liquid paraffin, petroleum products or silicone (of varying degrees of purity) into breast tissue (24, 26). In 1964, Miyoshi and colleagues (25) first described a possible relationship between connective tissue disease and paraffin injection. They reported two patients who developed disease many years after paraffin injections into their breasts. In one patient, the symptoms improved following a bilateral mastectomy. These authors suggested that the injected paraffin acted as an adjuvant in the pathogenesis of the disease (26), and proposed the term 'human adjuvant disease'. Currently, this term remains poorly defined, and its use has been strongly discouraged by the task force convened by the American Society of Plastic and Reconstructive Surgery (27).

In 1984, Kumagi and co-workers described a further 17 Japanese patients who developed connective tissue disease after foreign substance injection into breast tissue (24). Seven of the patients had received paraffin, eight had received silicone and two had received unknown substances. The mean time between surgery and connective tissue disease was 13.9 ± 5.4 years (range two to 22 years.) There were two groups of connective tissue disease patients. One group had autoimmune connective tissue disease: eight scleroderma (all

had received paraffin injections), three rheumatoid arthritis (all had received silicone injections). The other group had 'non-specific connective tissue disease' with a variety of symptoms. Two of four patients who subsequently had the injected substances removed showed subjective improvement after seven days, but this lasted only several months (24).

Kumagi (24) also reviewed the Japanese literature from 1964 to 1981, and found a further 28 patients who developed connective tissue disease following foreign substance injection. In 20 of the 28 patients, the nature of the substance was unknown. The mean interval between injection and onset of disease was 6.6 years. Again, there were two groups of patients. Kumagi also demonstrated that the risk of developing scleroderma was three times greater following the injection of paraffin (24). More recently, however, this increased prevalence has been questioned because, at that time, the exact number of patients receiving paraffin injections was poorly documented.

In 1982, Van Nunen and colleagues (28) first described a connective tissue disease syndrome in three patients following breast augmentation with silicone gel implants. Other authors have reported similar instances of connective tissue disease after gel implants (29,30). More recently, Vargas has reported a connective tissue disease syndrome in patients who had received saline-filled implants (31). In 1989, Varga and associates described four women who developed scleroderma six to 15 years after silicone gel implants (32). There was evidence of silicone leakage from the implants in these patients. Reports by other authors describe a 'latency' period, ranging from two years (28,31) to over 20 years (29), between implantation and the onset of connective tissue disease. In one study (32), this latency interval was reduced to 2.8 years after trauma to the breast and rupture of some of the implants. In 1993, Spiera and Kerr (34) described two patients who developed scleroderma three and 16 years after the insertion of silicone chin implants.

In some reports, clinical and laboratory improvement of connective tissue disease has occurred after the removal of silicone gel breast implants (34,35). Kaiser and co-workers described a 42-year-old woman who developed clinical and immunological features of systemic lupus erythematosus, 11 years after breast augmentation with silicone gel implants (35). Six months after explantation, her symptoms improved and her antinuclear antibody titres decreased from 1:1280 to 1:160 (35). In a further study, two of five patients with scleroderma, who subsequently had their implants removed, went on to "demonstrate marked improvement of their cutaneous disease" (34). Most of these studies of clinical improvement following implant removal are somewhat anecdotal.

Definition of connective tissue disease

Autoimmune connective tissue disease: The numerous case reports of patients developing well-defined autoimmune connective tissue disease after breast augmentation with injection or silicone gel implants have recently been reviewed by

Germain (23). Most of these patients carry the diagnosis of scleroderma. Other autoimmune connective tissue disease diagnoses have included rheumatoid arthritis, systemic lupus erythematosus and Sjogren's syndrome (36). In the normal population, the prevalence of these syndromes is: rheumatoid arthritis 1:100; systemic lupus erythematosus 1:500; and scleroderma 1:10,000 (37). In all of these diseases, there are well-defined clinical findings which have been set forth by the American College of Rheumatology (36-38). There are also specific laboratory tests to aid in the diagnosis of these conditions (36,39,40).

Non-specific connective tissue disease: Several reports of patients with silicone gel implants involve rheumatologic complaints that do not meet the American College of Rheumatology criteria for established rheumatologic conditions. These symptoms are usually nonspecific and include arthralgias, morning stiffness, nonspecific synovitis, malaise and fatigue (28,41-44). These patients usually have normal laboratory tests (28,41-44). Specific diagnoses in this group are less precise and may include fibrositis, polyarthritis, palindromic rheumatism and others. The diagnosis and prevalence of these conditions in control patients are also not well defined.

Epidemiologic studies – connective tissue disease

The main question concerning silicone gel implants and the development of connective tissue disease remains unanswered. Despite the many case reports throughout the literature, there have been no large scale epidemiological studies examining the relationship between silicone gel implants and connective tissue disease. There are two small studies in the plastic surgery literature (45,46). One is a retrospective review of 378 patients, of whom only 128 responded, and there was no cause-effect relationship between the implants and autoimmune disease (45). The other study was prospective and showed that two groups of patients (250 with gel implants and 353 with autologous tissue breast reconstructions) each had the same prevalence of an 'autoimmune syndrome' - one in each group (46). In the rheumatological literature, three controlled epidemiologic studies have been published (47-49). Dugowson and associates (47) studied 349 newly diagnosed female patients with rheumatoid arthritis and 1456 similarly aged control women from King County, Washington State. The patients with breast implants had no increased risk of developing rheumatoid arthritis (47). Gabriel and colleagues from the Mayo Clinic showed that 824 patients with breast implants did not have an increased risk of developing autoimmune connective tissue disease, when compared with 1634 control patients without breast implants (49).

Another method of investigating any potential relationship between scleroderma and silicone gel implants has been to assess the prevalence of breast implants in patients in scleroderma registries. If exposure to silicone gel implants causes scleroderma, these patients should be expected to have a higher proportion of implants than in the general population. In a preliminary study, Hochberg and colleagues (48) reported that only one of 140 (0.71%) female patients with

scleroderma and only 2.5% of 160 age-matched controls had received breast implants, indicating no significant relationship between breast implants and the development of scleroderma. A University of Toronto study showed that of 350 patients with scleroderma, only two had breast implants (50). One patient had saline implants and one had silicone gel implants. Both patients had early symptoms of scleroderma several years before they received their breast implants (50). There are two further studies from the United States. In one study of 725 patients with scleroderma, seven had received breast implants (12). In the other study of 3500 patients with scleroderma, 25 had breast implants (51). The implant rate of about 1% in these groups of patients parallels the rate of about 1% in all women (12).

Antibody studies

Antinuclear autoantibodies: The vast majority of patients with autoimmune connective tissue disease have elevated levels of antinuclear antibodies in their serum (36). Frequencies range from about 50% in rheumatoid arthritis and Sjogren's syndrome to almost 100% in systemic lupus erythematosus and scleroderma. In addition, there are certain specific types of antinuclear antibodies which have relative disease specificity (36,38-40,52). Several investigators have therefore studied the levels of these antibodies in patients with silicone gel implants.

A recent publication by Peters and colleagues (53) analyzed 200 consecutive patients with silicone gel implants, irrespective of any musculoskeletal or other complaints. This study demonstrated that 200 patients with silicone gel implants did not have elevated levels of antinuclear antibodies, when compared with a similar group of 100 age-matched control subjects without breast implants. In addition, 29 patients who had demonstrated implant rupture did not have elevated levels of these autoantibodies (53). These results suggest that women with silicone gel implants do not have a greater frequency of autoimmune phenomena than controls.

Bridges and colleagues studied 166 women with silicone gel implants who were referred to three rheumatologists with 'rheumatic complaints' (54). The patients were divided into three groups: 95 with arthralgias, myalgias and fatigue; 32 with 'mild arthritis'; and 29 with findings 'suggestive of connective tissue disease'. In the first two groups, which would correspond to the designation 'nonspecific connective tissue disease', the proportion of patients with elevated antinuclear autoantibody levels was not different from controls (54). A similar study was reported by Press and co-workers (55) of 24 patients with silicone gel implants who were referred to a rheumatology clinic with rheumatic complaints (55). Of 11 patients who had autoimmune connective tissue disease (scleroderma, systemic lupus erythematosus or rheumatoid arthritis), 10 had antinuclear autoantibody titres higher than controls. Of the 13 patients with 'non-specific connective tissue disease' (fibromyalgia, chronic fatigue syndrome, myalgias), five had elevated levels of antinuclear autoantibodies (55). Both of these reports failed to provide

any information about the frequency of development of connective tissue disease among women with silicone gel implants (36). Further, the likelihood of referral bias precludes any estimate of risk for women with silicone gel implants (36).

Anti-collagen autoantibodies: Teuber and colleagues (56) were stimulated by the hypothesis that patients with silicone gel implants could potentially develop host reactivity against components of the microenvironment around the implant, where type I collagen could be a major structural component. These authors demonstrated a significant increase in autoantibodies to both type I and type II collagen in the serum of patients with gel implants (56), when compared with control patients. The significance of this finding is being investigated further by this group.

Other antibodies: Goldblum and colleagues, using a modified enzyme-linked immunosorbent assay (ELISA), described two patients with ventriculoperitoneal shunts who developed specific immune reactivity to the elastomers of the silastic shunts (57). Both patients showed immunoglobulin (Ig) G binding to silastic tubing that was consistently higher than that of controls. The bound immunoglobulin appeared to represent specific antibodies to silicone (57). Wolf and co-workers (58) used a similar ELISA to assess blood samples from 160 patients with and without silicone gel implants. All 68 control patients in this study demonstrated measurable levels of anti-silicone IgG antibodies even though they did not have breast implants. The levels of these antibodies were significantly higher, however, in the 74 patients with breast implants ($P < 0.001$) (58). The significance of these elevated anti-silicone IgG antibody levels is currently being investigated.

Carcinoma of the breast

There appears to be no relationship between breast implants and the subsequent development of breast carcinoma. In a study of 3111 women in the United States, Deapen and colleagues (59) found nine cases of breast carcinoma, whereas 15.7 had been expected. A similar study of 11,676 patients in Alberta showed that 41 patients had developed breast cancer, whereas the expected number was 86.2 cases (60). A further study by Birdsall and colleagues from Alberta

(61) demonstrated that women with breast implants in whom breast cancer developed were not diagnosed at a later stage, and did not experience an impaired survival, compared with breast cancer patients without implants. A further 13-year study of 12 patients who had developed breast cancer coexistent with free silicone in the breast (nine from silicone injections, three after implant leakage), did not show any causal relationship between free silicone and carcinoma development (62).

One type of implant, the Meme prosthesis, which is coated with a polyurethane foam covering (in an attempt to reduce capsular contracture and breast firmness), has been shown to degrade into 2,4-toluene diamine. This substance has been shown to cause sarcoma in laboratory animals in one model (63). Although this implant was removed from the market in Canada in April 1991, its use in humans has not been reported to be associated with the development of breast cancer. Sinclair and colleagues (64) recently analyzed 75 polyurethane-covered implants and their surrounding capsules, using scanning electron microscopy and light microscopy. This study confirmed degradation of the polyurethane. In fact, the polyurethane foam had undergone sufficient biodegradation by three years to lose its structural integrity. The significance of this degradation remains unknown.

SHOULD SILICONE GEL IMPLANTS BE REMOVED FROM PATIENTS?

At present, there are no conclusive data that silicone gel implants – whether intact or non-intact – are related to the development of any medical disease. The FDA has stated that there is currently no indication to remove routinely silicone gel implants from patients. The FDA has recommended, however, that broken implants be removed. The gel was originally intended to be contained within a solid elastomer shell. If the gel is no longer contained in this shell, intuitive reasoning would support this recommendation for removal.

If a silicone gel implant is found to be leaking or ruptured, should the capsule be removed? On the one hand, it seems reasonable to eliminate any residual potential foreign body reaction. On the other, capsulectomy certainly can add further significant morbidity and can result in breast deformities, particularly in patients with only a small amount of breast tissue.

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