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Do silicone breast implants cause connective tissue disease?

There is still no clear evidence that they do

See p 417

Few more controversial issues exist in modern rheumatology than the putative association between silicone breast implants and systemic connective tissue disease. The term silicone refers to a family of chemically related organic silicon compounds derived from silica (SiO_2). Small quantities of silicone are found in joint prostheses, artificial heart valves, and baby bottle nipples, but the major medical use of the fluid compound, polydimethyl siloxane, is in implants. Silicone breast implants were developed in 1962 and are used mainly for cosmetic augmentation (80%) and reconstruction after surgery for breast cancer.[1] By 1992, 1-2.5 million women had received such implants in north America,[2] and 100 000-150 000 British women are currently estimated to have them. Silicone implants have been associated with hardening (thought to be due in part to leakage), occasional rupture, and enlargement of lymph nodes draining the implant site.[3] It is the possible link with systemic connective tissue diseases, however, that has fuelled an acrimonious medical, regulatory, and legal debate.

Although the first report of a connective tissue disease after direct injection of silicone into the breast dates from 1964,[4] the first three patients with silicone implants who developed these disorders were documented in 1982.[2] Since then over 290 patients have been described in the English language literature.[2] Although the most common specific diagnosis is scleroderma, a range of disorders has been reported, and many cases had a non-specific syndrome that did not fulfil conventional clinical and laboratory criteria for particular connective tissue disorders.

Public awareness of the issue rose steeply in 1991, when an American jury found that a patient had contracted mixed connective tissue disease as a result of her breast implants and that the company had misrepresented the safety of the product. In response to these events, and after two independent advisory panel reviews, the Food and Drug Administration requested a moratorium on the use of implants other than within trials.[5] By 1994 manufacturers of the implants had earmarked a large fund to deal with the burgeoning number of legal claims while still maintaining that the evidence did not link them to systemic disease. The litigants were given a deadline by which to choose between joining a large class action which guaranteed a minimum settlement, abandoning their litigation, or litigating separately. The first of these options became the then largest proposed product liability settlement in American legal history.

Compensation for women outside the United States was set well below that for American women and has since been complicated by the chapter 11 bankruptcy of one of the manufacturers. Many women have continued to pursue individual claims. In Britain a Department of Health advisory group reported in 1994 that there was no evidence of an increased risk of connective tissue disease in patients with silicone breast implants and no scientific case for changing practice or policy with respect to breast implantation.[6]

Given this highly charged medicolegal background, what is the evidence that silicone breast implants cause connective tissue disease? Initial analyses used published case series to estimate the cumulative incidence of connective tissue disorders among women who received implants and suggested that the incidence estimates were similar to those expected in the general population.[2] These were supplemented by several case-control and cohort studies. Reviews of these studies have highlighted methodological shortcomings: in particular, the definition of connective tissue disease (and its validation) varies widely, and many studies are small, lacking statistical power.[7]

Of the larger studies, only one points to a weak association: this retrospective cohort study of 395 543 American female health professionals who completed a self administered questionnaire reported a relative risk of any connective tissue disease in association with previous implant surgery of 1.24 (95% confidence interval 1.08 to 1.41).[8] The study's major limitation was uncertain diagnostic validity, with potential bias due to differential over-reporting. The authors themselves concluded that silicone implants were unlikely to be associated with a substantial excess risk of major connective tissue disease. A second retrospective cohort study of 749 women who had received implants and 1498 community controls, followed for an average of 7.8 years, found no association between breast implants and connective tissue disease diagnosed at review of the medical record.[9] The Nurses Health Study, which used information collected through biennial mailed questionnaires, also failed to find an association.[10] Finally, a meta-analysis of the epidemiological studies performed to date has also been negative.[11]

The paper by Nyren et al in this issue adds to this body of evidence (p 417).[12] They report a retrospective

BMJ 1998;316:403–4

cohort study of women included in the Swedish national inpatient register. They compared first hospitalisation rates for connective tissue diseases between 7442 women with implants and 3353 women who had undergone breast reduction surgery over 92 880 person years of observation. No significant increase in risk of connective tissue disease was apparent when rates in the implant group were compared with expected rates in the general population (standardised hospitalisation ratio 1.1; 0.8 to 1.6) or with those in the breast reduction group (1.3; 0.7 to 2.2). Careful attention was paid to validating diagnoses, and the use of admission rather than self reports of disease improves specificity. The results add weight to the conclusion that silicone breast implants are not associated with a meaningful excess risk of connective tissue disease.

It is difficult to see how epidemiological studies will shed more light on this vexed issue. Some of those concerned in prolonged legal disputes are clearly unshakeable in their belief that the association exists, and the public reputation of silicone breast implants may have been irrevocably tarnished. An independent review group of the Department of Health, established by the chief medical officer in response to ministerial concern, is due to report this spring. Until then perhaps the medical community's most appropriate response would be to endorse the American College of Rheumatology's plea that greater reliance should be placed on the quality of evidence during the early appraisal of health issues such as this.

Cyrus Cooper *Professor of rheumatology*
Elaine Dennison *Wellcome training research fellow*

MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD

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Neonatal screening for cystic fibrosis

No evidence yet of any benefit

Neonatal screening for cystic fibrosis by using a simple test that can be performed on the "blood spots" routinely collected in screening for phenylketonuria and hypothyroidism raises exciting possibilities. The test is relatively easy to perform and the specimen is already collected, but even a simple test performed on millions of individuals will be costly, and the early knowledge of a serious disorder will cause more harm than good if there is no effective remedy. The results of a large randomised trial of neonatal screening for cystic fibrosis have recently been published in the *New England Journal of Medicine*.[1] The trial involved two thirds of a million newborn infants and their subsequent follow up. The conclusion that screening and subsequent treatment improves the growth and development of children with cystic fibrosis was met with enthusiasm.[2] Unfortunately the conclusion may not be justified, and the results suggest that any long term benefit is small.

The neonates were randomised into two equal groups of about 325 000 and immunoreactive trypsinogen measured on the blood spots of all infants; towards the end of the study DNA testing was also performed. In the "screened" group the results were examined immediately and acted on if they were positive. In this group there were 74 cases of cystic fibrosis (15 with meconium ileus recognised at birth, 54 detected by screening, and five missed on screening but diagnosed later clinically). In the control group the trypsinogen results were stored and examined when the child was 4 years old. In this group there were 67 cases of cystic fibrosis (18 with meconium ileus recognised at birth, 40 who presented clinically before the age of 4, and nine who were diagnosed only when the trypsinogen results were examined at the age of 4). The expectation of benefit from screening can only be small because the median age at diagnosis was 23 weeks in the controls, only 16 weeks later than in the screened group. Screening materially advanced diagnosis in only a minority.

The weights and heights of the two groups are reported in the paper. A difficulty that is not discussed in the report is that the data in children under 4 years are subject to selection bias. On average, affected infants in the screened group are likely to be healthier than identified affected infants in the control group, because the affected infants in the screened group are likely to include infants with less severe disease that would not have presented clinically had they not been screened. Only after 4 years are the two groups, in expectation, comparable, and only after this point does the randomised design ensure the avoidance of bias. The conclusion by the authors that screening is associated with taller and heavier children rests on the results

BMJ 1998;316:404–5