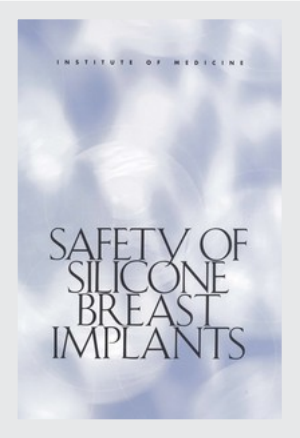

Safety of Silicone Breast Implants (1999)

DETAILS

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Effects on Pregnancy, Lactation, and Children

It has been suggested that children born to, and breast-fed by, mothers with silicone breast implants might be adversely affected by transmammary or transplacental delivery of silicone during either breast feeding or pregnancy. Silicone might be available for transmission since periprosthetic breast tissue, regional lymph nodes, and possibly more distant sites in such women are exposed to silicone fluid by gel fluid diffusion, to silicone gel in cases of implant rupture, and to silicone elastomer from implant shells. Mothers with breast implants might also have problems with breast feeding due to the effects of implant surgery, the implant itself, or fear of lactation insufficiency and transmission of complications to their infants. The committee has reviewed the effects of breast implants, especially silicone gel breast implants, during pregnancy and lactation.

EFFECTS OF SILICONE BREAST IMPLANTS DURING PREGNANCY

The ability of silicone to pass the placental barrier depends on factors such as the size of the silicone molecule. The concentration gradient of silicone in the maternal and fetal circulation is also important. This gradient in turn is dependent on other factors, including the amount of silicone in the maternal–fetal circulation, the protein-binding ability of silicone, and the uterine blood flow. Whether silicone crosses the placenta has not been evaluated in women, but there is little evidence of any elevation of

blood or serum silicon or silicone concentrations in women with silicone breast implants, and elevations reported in two studies have been modest and have not been confirmed by subsequent studies (see below and Chapter 5 of this report).

The committee is not aware of any studies of reproductive or teratologic effects of silicone in humans. However, reproductive and fetal developmental effects of polydimethylsiloxane (PDMS) fluid have been evaluated in rats and rabbits, and mutagenic potential was evaluated in mice. Teratologic and mutagenic effects were not observed at the dose levels and in the species employed (Kennedy et al., 1976). Subcutaneously implanted silicone elastomer and silicone gel at several dose levels did not induce maternal or developmental toxicity before or during pregnancy and lactation, did not have adverse effects on parents or neonates, and did not impair reproductive performance in either male or female rats or pregnant female rabbits (Siddiqui et al., 1994a,b). These and other relevant studies are reviewed in Chapter 4. Evidence from these studies for toxic effects of silicone during or after pregnancy is lacking.

EFFECTS DURING LACTATION

Effect on Breast Milk

Many drugs and chemicals that appear in the maternal circulation may be detected in breast milk (Berlin, 1989). Characteristics that affect a compound's ability to traverse the mammary gland epithelium, appear in human breast milk, and become available to a nursing infant include its degree of ionization, molecular weight, lipid solubility, and protein-binding capacity. Except in the rare event of direct rupture of a deposit of silicone into a milk duct (Leibman et al., 1992; Shermis et al., 1990), to be transferred to breast milk, silicone must diffuse or be transported across a number of cell membranes. The evidence reviewed in Chapter 4 does not support diffusion or transport of silicone gel across membranes that presumably would exclude substances of high molecular weight. The evidence does suggest limited mobility of lower molecular weight linear or cyclic species, but these compounds are present in very low concentrations in breast implants, do not appear to be highly mobile in experimental distribution studies, and are subject to the body's clearance mechanisms.

Some proteins from maternal or external sources have been found in milk—for example, cows' milk proteins and maternal immunoglobulin G (IgG)—and these proteins can be found in the serum of breast-feeding infants. Transport of these proteins probably occurs through clefts between mammary alveolar cells (Berlin, 1989). Most other proteins do not

cross from maternal circulation into breast milk. Ions, such as sodium and iron, do not cross well either, except for those such as lithium, with low atomic weights.

The determination of silicon or silicone in human body fluids by current technologies is discussed in Chapter 5. Reported blood and tissue measurements are reviewed there, as are the problems in attaining accurate and reproducible results and the varied sources of silicon and silicone that either contribute to dietary intake and affect biological concentrations or constitute environmental contaminants in analytical measurements. In addition, Chapter 5 notes that analyses of tissue and body fluid samples usually measure concentrations of the element silicon and do not differentiate between inorganic and organic (silicone) silicon-containing compounds.

Although, as noted earlier, silicone could enter breast milk through direct extension from deposits in breast issue, there is no evidence that this is other than a rare event, and it has not been reported in breast-feeding women with implants. Measurement of silicon or silicone concentrations in breast milk of women with implants might provide some insights into whether silicone reaches breast milk by other means. Jordan and Blum (1996) reported silicon measurements from a U.S. laboratory in 69 breast milk samples by inductively coupled plasma atomic emission spectrometry. The implant status of women providing these samples was not mentioned, but all showed a silicon concentration of less than the detection limit, 0.05 μg/ml. Tanaka et al. (1990) reported breast milk silicon concentrations in healthy postpartum Japanese women without implants averaging 0.171 μg/ml and serum concentrations of 0.27 μg/ml. These higher results may be due to an increased intake of silicon in the high-fiber, high-silicon diet of the Japanese population; they may also reflect the known, ubiquitous analytical problems caused by contamination with environmental silicon (Semple et al., 1998). In a Dow Corning laboratory, no difference was found between breast milk samples (1.2 parts per million [ppm]), control samples (2.1–3.9 ppm), and water blank (0.4–3.1 ppm) samples. These outlier results undoubtedly reflect analytical difficulties as the authors note (Curtis et al., 1991).

In a study of breast milk from women with silicone breast implants compared to controls, no significant difference was found. Breast milk was tested for silicon concentrations in 10 women with silicone gel breast implants (0.063.7 ± 0.041 μg/ml) compared to 20 women without breast implants (0.061 ± 0.035 μg/ml) measured by graphite furnace atomic absorption spectrophotometry (Lugowski et al., 1996; and personal communication, 1998). In a later report, Lugowski et al. (1998) compared breast milk and blood silicon concentrations in 14 and 15 blood and milk samples, respectively, from women with silicone gel implants and 23 and

29 blood and milk samples, respectively, from women without implants. Mean blood concentrations were 0.0743 and 0.1038 μg/ml, and mean milk concentrations were 0.0587 and 0.0511 μg/ml in women with implants and control women, respectively. There were no significant differences in blood or milk silicon concentrations between these two groups (Lugowski et al., 1998). In yet another report from the same laboratory comparing 15 lactating women with silicone breast implants to 34 lactating control women, mean silicon concentrations in breast milk were 0.0555 ± 0.035 and 0.0511 ± 0.031 μg/ml, respectively, and in blood were 0.0793 ± 0.087 and 0.10376 ± 0.112 μg/ml, respectively. The mean silicon concentration measured in store-bought cows' milk was 0.7089 μg/ml and that for 26 brands of commercially available infant formula was 4.4025 μg/ml (Semple et al., 1998). These last three studies taken together suggest that lactating women with silicone breast implants are similar to control women without implants with respect to the concentrations of silicon in their breast milk and blood. Silicon concentrations in cows' milk exceed concentrations in human breast milk by a factor of ten and are even higher in infant formula. Five different samples of cows' milk yielded silicon concentrations ranging from 0.667 to 0.778 μg/ml. Even higher concentrations of silicon were measured in 26 brands of infant formula (0.796–13.796 μg/ml). The high values for silicon in cows' milk and infant formula found by Semple et al. (1998) do not necessarily imply a high silicone content, however. There are likely multiple sources of both silicon and silicone in processed and manufactured foods, which may be related to silicon in cows' feed, silicone antifoaming agents, or packaging techniques involving silicone, among other factors. The results from this laboratory appear to represent accurate values since collection of samples was scrupulously controlled to avoid contamination and samples were prepared in a class 100 "ultraclean" laboratory.

Although only modest numbers of women were enrolled in these studies, breast milk from women with silicone implants appears to have a relatively low concentration of silicon, especially when environmental forms of silicone and silicon are accounted for. Breast milk concentrations may reflect blood silicon concentrations and, as noted earlier, may therefore be in large part inorganic, although as noted earlier, women in industrialized countries have ample exposure to silicone in a number of ways (Adler and Berlyne, 1986). Semple et al. (1998) have also demonstrated that two alternatives to breast milk, cows' milk and infant formula, contain considerably more silicon than breast milk. Infants may have significant exposure to silicone in infant formulas, cows' milk, bottle nipples, and infant pacifiers. Silicone, as a component of Simethicone-containing proprietary drops, is also considered safe and effective as a treatment for colic or gastrointestinal hypermotility in infants and children. One such

product (Mylicon) contains 67 mg of PDMS/ml (Berlin, 1994). The committee concludes that there is convincing evidence that infants breast-fed by mothers with silicone gel breast implants receive no higher silicon intakes from breast milk than infants breast-fed by mothers without breast implants. Infants receiving cows' milk or commercial infant formula feedings are likely to have significantly higher silicon intakes than breast-fed infants. Evidence that any likely exposure to silicon or silicone has effects on infant health is lacking. The proportion, if any, of silicone in measurements of silicon in the samples discussed remains to be investigated. The oral toxicity of methylated siloxanes is very low, however, and these siloxanes are generally recognized as safe (for oral exposure) by the Food and Drug Administration (FDA) when used as indirect food additives as reviewed in Chapter 4 of this report (D. Benz, FDA, personal communication, 1998).

Breast Implants and Problems with Breast Feeding

Under the influence of rising concentrations of estrogen, progesterone, and prolactin during pregnancy, the breast increases in water, fat, and electrolyte content. The overall increase in breast volume is approximately 0.75 pound per breast. This increase in size may cause breast discomfort in women who have implants, especially those with capsular contractures, i.e., beyond the discomfort normally experienced by pregnant women (Lawrence, 1989; Riordan and Auerbach, 1993).

The prevalence of breast-feeding problems in the general population is not well defined, but both maternal and infant factors account for the cessation of breast feeding or for lactation insufficiency. Although insufficient milk supply is the major reason reported by mothers for early termination of breast feeding in both developed and developing nations (Gussler and Briesemeister, 1980), other maternal factors may contribute to insufficient milk supply such as sore nipples, let-down reflex inhibition, engorgement, blocked milk ducts, infection and return to work. Infant problems also are related to insufficient supply of breast milk, for example, poor weight gain (Hill and Schatten, 1991; Melnikow and Bedinghaus, 1994).

Few studies have evaluated women with silicone breast implants during pregnancy. In the survey by de Cholnoky (1970) of 265 plastic surgeons and 10,941 breast augmentation procedures (including 149 silicone injections and 6,304 silicone gel, Cronin-type implants), plastic surgeons reported that women tolerated implants without significant complaints during pregnancy and nursed babies adequately. Whidden (1986), in a report of 2,228 women who had breast augmentation procedures with either silicone gel- or saline-filled implants, noted that problems

with breast feeding were not encountered. The value of these reports is limited since no information is provided on the number of women who breast-fed their infants, the duration of breast feeding, any problems they might have had, or how women were evaluated for lactation sufficiency. In the epidemiological study of children of women with silicone breast implants in Denmark discussed below, there was incomplete information on breast feeding (Kjoller et al., 1998).

Three studies have focused on the effects of augmentation mammaplasty on lactation sufficiency. Neifert et al. (1990) studied 319 first-time mothers who breast-fed healthy, full-term infants. Although the relative risk of lactation insufficiency was threefold greater for women with a history of breast surgery (95% confidence interval [CI], 1.65–5.9), only 5 of the 22 surgeries were for breast augmentation with implants. Surgery with a periareolar incision was almost five times more likely to be associated with insufficient milk compared to no surgery. Breast incisions in other locations were not associated with lactation insufficiency (Neifert et al., 1990). Hurst reported retrospectively on 42 mothers with breast implants for augmentation and 42 mothers without implants matched for age, delivery type, breast-feeding experience, and other factors, who were selected from 5,066 mother–infant records from a Texas hospital. Both groups of mothers received the same intensive lactation support and counseling from a hospital-based lactation program. The frequency of lactation insufficiency was significantly increased in women with implants (27 out of 42, 64%) compared to women without implants (3 out of 42, 7%). Periareolar incision was most associated with breast-feeding insufficiency, although the frequency of lactation insufficiency in augmentation by the submammary or axillary approach was statistically significantly increased compared with women without implants. No data were available on the type of implants (Hurst, 1996).

In a survey of 292 women with saline-filled breast implants, 46 women reported subsequent pregnancies and 28 chose to breast-feed their infants. Breast-feeding problems were reported by 11 of the 28 mothers with implants (39%), and 8 of these women reported problems related to lactation insufficiency (28%): 4 nipple problems and 4 milk production problems. Seven of these women had periareolar incisions. (About 30% of breast implant augmentations are carried out through a periareolar incision; ASPRS, 1997.) The women who chose not to breast-feed (18 out of 46) reported fear of lactation insufficiency and other complications due to the implants as the primary reason (Strom et al., 1997). In addition to these reports, Peters et al. (1997) noted in a study of 100 consecutive women who were having silicone gel implants removed, that 19 of 75 women responding to a questionnaire reported successful breast feeding;

it was not clear how many of the 75 had completed pregnancies and attempted breast feeding, however.

These studies primarily describe retrospectively small cohorts of mothers with implants. Only one study involved a matched comparison group, and the type of implant was specified in only one study, although most of the women in the other two reports probably had gel-filled implants, given the usage of implants for augmentation at the time of the study. These studies did not measure the frequency of infections or mastitis, either, although Hurst (1996) reported on multiple correlates of lactation insufficiency. These studies suggest that there is no difference in age, ethnicity, delivery type, smoking history, or breast-feeding experience among women with breast implants and those without implants, but as many as 64% of women with implants may have lactation insufficiency compared to less than 10% of women without implants (Hurst, 1996). Based on these studies, the relative risk of lactation insufficiency is at least three times greater in women who have a history of breast surgery, and the risk of lactation insufficiency increases with a periareolar incision (Hurst, 1996; Neifert et al., 1990; Strom et al., 1997). Periareolar incisions may be more likely to sever lactiferous ducts, depending on operative technique.

Breast-feeding problems appear to be common in women with either silicone or saline implants. The frequency of lactation insufficiency ranges from 28 to 64% for both silicone gel- and saline-filled implants. Women with breast implants have also been less likely to attempt breast feeding due to their fear of problems stemming from the implant (Crase, 1996). Although the data on periareolar incisions and lactation are suggestive, the mechanism of increased lactation problems due to implants remains uncertain; Hurst (1996a) suggests that pressure exerted by an implant may be detrimental to milk production. Increased intramammary pressure, when prolonged and unrelieved, may cause atrophy of the alveolar cellular wall and diminished milk production. The location of the implant might also be a factor. Implants in the submuscular position might exert less pressure or in other ways interfere less with functioning glandular tissue.

In addition to the reports discussed above, six studies report eight cases of abnormal lactation or lactation complications (mastitis, galactorrhea, or galactocele formation) after breast implant surgery (DeLoach et al., 1994; Hartley and Schatten, 1971; Johnson and Hanson, 1996; Luhan, 1979; Mason et al., 1991; Menendez-Graino et al., 1990). Galactocele and galactorrhea after breast augmentation surgery are uncommon complications based on these reports published over a 14-year time span. The eight cases included both saline implants and gel-filled implants. Although these case reports describe complications related to lactation, the preva-

lence of these complications cannot be adequately assessed. Furthermore, information is lacking in a number of studies, such as the type of breast implant or the type of surgical incision.

Based on the information available, the type of implant does not appear to be related to postpartum breast infection or abnormal lactation. The cause of galactoceles remains unknown, but postoperative breast congestion around the implant may trigger the release of lactogenic hormone and thereby stimulate milk production and secretion. Oxytocin or prolactin release may be stimulated either hormonally, by direct pressure on the breast, or both, and substantial increases in serum prolactin have been measured in women after breast stimulation (Kolodny et al., 1972). The majority of these women will require removal and replacement of their implants along with hormonal medication to suppress the galactorrhea.

Breast Feeding in the United States: Prevalence and Advantages

In the United States, the prevalence of breast feeding at one week postpartum was 52% for hospital-born infants in 1989, and only 18% still were receiving breast milk by 6 months of age (Riordan and Auerbach, 1993). In general, breast feeding is more common among older Caucasian women of higher socioeconomic status. The World Health Organization, the UNICEF, and the U.S. Public Health Service (Surgeon General) have established national and international goals to promote and support breast feeding (Riordan and Auerbach, 1993; U.S. DHHS, 1991). The Surgeon General's nationwide objective proposes to increase the proportion of women who are breast feeding their infants at hospital discharge to 75% and the percentage of women still breast feeding infants at 6 months of age to 50% by the year 2000. One study provides data on the prevalence of breast feeding in women with breast implants (Strom et al., 1997). In this survey discussed earlier, 61% of women with breast implants chose to breast feed, suggesting that the prevalence of attempted breast feeding by women with implants approximates its prevalence in the general population.

The distinct advantages of breast feeding and breast milk are widely appreciated. Breast feeding plays an important role in human infant development. Breast milk provides not only essential nutrition for the infant but also protection against infections and other immunologic disorders. Gastrointestinal disease, respiratory ailments and asthma, otitis media, and allergies occur less frequently in breast-feeding infants (Castello, 1986; Lawrence, 1989; Riordan and Auerbach, 1993). Although more speculative, breast feeding is also said to provide protection against obesity, arteriosclerosis, celiac disease, and other metabolic disorders (Hanson et al., 1985; Lawrence, 1989; Mayer et al., 1988). With respect to the mother,

breast feeding creates a psychological bond between infant and mother, which ultimately may lead to a socially healthier child (Newton and Newton, 1967). In addition, lactation enhances maternal postpartum recovery, and body weight returns to prepregnancy levels more rapidly (American Academy of Pediatrics, 1997). The committee believes that breast feeding should be encouraged in all mothers when possible, including those with silicone breast implants. There is evidence that breast implantation may increase the risk of insufficient lactation, but no evidence that this poses a hazard to the infant beyond the loss of breast feeding itself. The evidence for the advantages of breast feeding to infant and mother is conclusive.

EFFECTS ON CHILDREN

In the early 1990s, claims were made that children of women with silicone breast implants might be adversely affected by transmammary or transplacental delivery of silicone during breast feeding or pregnancy (Gedalia et al., 1995; Levine and Ilowite, 1994; Teuber and Gershwin, 1994). Hypotheses were advanced that silicone transmitted in breast milk might cause an autoimmune or connective tissue disease in children of mothers with breast implants; that maternal autoantibodies resulting from exposure to silicone in breast implants might be transferred to children across the placenta or in breast milk; or that silicone-induced immunological abnormalities, other than autoantibodies, in mothers with breast implants might be transmitted to their children across the placenta or in breast milk. The committee finds no evidence for these hypotheses.

Connective Tissue or Autoimmune Disease and Esophageal Effects

Two case series from California (Teuber and Gershwin, 1994) and New York (Levine and Ilowite, 1994) proposed that signs and symptoms found in children whose mothers had silicone breast implants were suggestive of autoimmune disorders. Teuber and Gershwin (1994) described one female child of each of two mothers who had breast implants (one ruptured, one suspected to have ruptured), positive antinuclear antibodies (ANA) and arthralgia or arthritis. Both children, one 3 and one 9 years of age, had longstanding myalgia. Both were found to have antinuclear antibodies (titers of 1:40 and 1:80, respectively), and the 9-year-old girl had high-titer antibodies against denatured human type II collagen. These children were normal on physical examination except for diffuse tenderness of the lower back, abdomen, and muscles of the extremities in the 9-year-old (Teuber and Gershwin, 1994).

Levine and Ilowite (1994) suggested a link between esophageal symptoms found in breast-fed children and maternal silicone breast implants.

Although labeled as a case control study by the authors, sample reduction procedures in the experimental and control groups attenuate this study to a case series of eight breast-fed children and three bottle-fed children. (A correction making this change was published by Journal of the American Medical Association, 272 (10): 770, 1994.) Physician or support groups referred mothers with silicone breast implants who were concerned about the effects of these implants in their children. Of 67 children born to these women, 56 were breast-fed and 11 were bottle-fed. No data were provided on the health histories or status of this original sample. The sample was reduced to 43 children with recurrent abdominal pain and then, for unclear reasons, further reduced to 26 children with additional symptoms such as vomiting, dysphagia, decreased weight–height ratio or a sibling with these complaints. Family permission was not obtained for 15 of these 26 to participate in this study. The final sample included 11 children (6 boys and 5 girls), from 18 months to 13 years of age, 8 breast-fed and 3 bottle-fed. The average duration of breast-feeding was five months, and the mean interval between discontinuation of breast-feeding and evaluation was 5.7 years. The average age of the breast-fed children was 6 years (18 months to 9 years), and of the bottle-fed children was 5 years (18 months to 13 years). These 11 children were compared to patients (11 boys and 6 girls; average age, 10.7 years) from a control group of 20 patients with feeding problems reduced to 17 by excluding 3 patients with achalasia. Six of the eight breast-fed children from mothers with silicone breast implants were reported to have significantly abnormal esophageal motility with nearly absent peristalsis in the distal two-thirds and decreased lower sphincter pressure based on esophageal manometry and upper-intestinal endoscopy with esophageal biopsy. Compared to controls, the breast-fed children were said to have significantly decreased lower sphincter pressure and abnormal esophageal wave propagation. No gross endoscopic findings or histologic evidence of infection or deposits of silicone were observed among any of the children. Levine and Ilowite (1994) speculated that their findings provided support for a scleroderma-like esophageal disease in children breast-fed by mothers with silicone breast implants.

The committee notes a number of problems with this study. The unexplained reductions in the study groups raise questions of selection bias as does the refusal to participate of 15 of 26 (58%) children in the final sample. Parents and children may have been influenced to focus on esophageal symptoms by the emphasis on these symptoms in a questionnaire circulated to enlist the experimental group. Many data gaps exist in reporting signs, symptoms, and clinical laboratory findings in the original and subsequent experimental groups of children and mothers. Apparently the children did not fulfill any of the criteria for scleroderma, in-

cluding positive autoantibodies; information of this sort was not given for the mothers. No data on the type or status of implants in the mothers were provided. The control group was also reduced and is inappropriately age matched, raising issues of age differences in use of technology to evaluate esophageal function and in the response to sedation used to enable examination. These may be important considerations (Hillemeier, 1986). Bartel examined one of the original breast-fed children and suggested a separate neurological cause for the esophageal findings (Bartel, 1994). One analysis of the six breast-fed cases with abnormalities suggested that they might all have come from just two families, which would limit the generalizability of these findings. Why the three original bottle-fed children in the study sample were not controls instead is not clear if the variable at issue was the effect of breast feeding, as the title of this report indicates. If the variable under study was simply the presence of breast implants, then these three children provide no evidence that breast implants are associated with abnormalities of esophageal function in children. Many of these concerns have also been noted by others (Bartel, 1994; Berlin, 1994; Brody, 1994a; Cook, 1994; Epstein, 1994, 1996; Flick, 1994; Liau et al., 1994; Placik, 1994).

The authors of both of these case reports speculated that the symptoms and findings in these children might, in fact, be due to exposure to silicone in breast milk or in utero or to transmission of some undefined immunological factor(s) from the mothers. No assays for silicon or silicone were performed, however, in any of the mothers or the children. As noted earlier in this chapter, silicon concentrations in breast milk of mothers with implants are not elevated above concentrations in lactating control women without implants. As reported in Chapter 5 as well as in this chapter, silicon concentrations in blood or serum of women with silicone breast implants are the same as concentrations in normal or lactating control women (Lugowski et al., 1998; Semple et al., 1998), with the exception of two reports of nonlactating women, which found somewhat higher than normal controls, but still quite low concentrations (Teuber et al., 1995a, 1996; Peters et al., 1995a). The highest silicon concentrations—orders of magnitude higher—are found in cows' milk and infant formula (Semple et al., 1998). If breast milk is a key factor in effects in children, these findings do not identify a cause; they provide evidence against elevated silicone as a causative agent in human breast milk.

With the exception of low- to moderate-titer, nonspecific ANAs in the mothers of the two girls reported by Teuber and Gershwin (1994), no immunological abnormalities were found in the mothers of these children. Since antinuclear antibodies are not infrequently found in normal women of childbearing age, it is difficult to assign any significance to them in these cases (see Chapter 7 of this report and, for example, Yadin

et al., 1989). Some of the children reported had nonspecific ANAs, but most did not. One child had anticollagen antibodies, as noted. No other immune abnormalities were found in these children, and in the case of esophageal abnormalities as noted above, the children of mothers with breast implants who were bottle-fed did not display abnormal esophageal motility providing no evidence that some other, possibly immune factor might be at work in these mothers and children.

In a two-year follow-up to their original report, Levine et al. (1996) reported on the original eight plus three additional similarly breast-fed children. Although the children were reported to be in better general health, the esophageal findings were essentially unchanged. The original bottle-fed children were not reported again. Macrophage activation was measured by urinary nitrates and neopterin as an indication of a hypothesized silicone-induced inflammatory process, and the effect of treatment using ranitidine (4 mg/kg per day, an inhibitor of stomach acid secretion) was evaluated. Endoscopic examinations revealed mild esophagitis in eight of ten children, with four normal biopsies and six biopsies showing inflammation. Urinary nitrates were not significantly different from the initial determination, but urinary neopterin levels had decreased. The authors concluded that esophageal dysmotility was chronic in children breast-fed by mothers with silicone breast implants and that prokinetic agents (like ranitidine) might be useful in treatment (Levine et al., 1996). This follow-up study suffers from many of the problems of the first. Three new cases were added with almost no additional data. Very little information on the general health status of any of the children is provided. There is no discussion of the control of dietary nitrates, which could influence urinary nitrate measurements. Intercurrent infections and even immunizations can result in urinary neopterin concentrations an order of magnitude greater than those observed here (Fuchs et al., 1992).

An attempt was made to investigate the effect of maternal silicone gel implants on esophageal pathology in breast-fed rat pups. Silicone gel was injected beneath the nipples of Sprague-Dawley rats, which were subsequently bred. Some of the resulting pups breast-fed without further intervention, and some breast-feeding pups received an injection of 2 ml of silicone gel in the neck as a further challenge. The esophagus of each pup at intervals up to 64 weeks was examined by a variety of light and electron microscopic techniques. No silicone was found in any esophagus, and no esophageal fibrosis was observed. In this study, silicone did not accumulate in the esophagus, and no esophageal pathology was seen (Raso et al., 1997).

Since esophageal problems or decreased esophageal motility have not been found in bottle-fed children of women with silicone breast implants, any consequences for esophageal function appear to be related to

breast feeding. The committee can not imagine, and finds no evidence for, any immune mechanism associated with breast milk that would produce esophageal or immune–autoimmune changes a decade after breast feeding. Also, in the absence of any finding of elevated silicon or silicone in breast milk of mothers with implants or accumulating in the esophagus or elsewhere in the bodies of these children or in the esophagus of an experimental rat model, the committee has not found evidence that silicone could produce esophageal changes years after birth. No biologically plausible mechanism for an immune or silicone effect in breast milk associated with esophageal changes is apparent to the committee or has been suggested by others. Finally, as discussed later in this chapter, a well-designed epidemiological study provides no support for an association of esophageal disease in children with silicone breast implants in their mothers.

Immunological Studies

A number of studies have proposed immune effects in children of mothers with breast implants. As noted earlier, Levine et al. (1996) measured urinary nitrites or nitrates and neopterin as proxies for macrophage activity and reported that some children breast fed by mothers with silicone implants, and in particular children with esophageal symptoms, had elevated urinary concentrations of these substances. They also reported that concentrations varied inversely with esophageal wave propagation and with age, suggesting a relationship with esophageal dysfunction and a waning of the infant effect as the children age (Levine et al., 1996). Because nitrate intake was not controlled and neopterin concentrations are intensely variable under a number of different circumstances as discussed earlier, these results are difficult to interpret in this highly selected population. There is also no evidence that the putative causative exposure to silicone actually occurs.

Maternal antibody transmission from a mother with silicone breast implants to her child, with a presumed health consequence, was reported by Gedalia et al. (1995). In this case, the infant presented with positive anti-Ro antibody and skin rash. Similar instances of neonatal systemic lupus erythematosus (SLE) with anti-Ro autoantibodies transmitted from a mother with SLE and anti-Ro antibodies were discussed. From time to time, cardiac sequelae are observed. In this infant, the antibody and rash cleared by 1 year of age (Gedalia et al., 1995). Levine et al. (1996) measured antinuclear antibodies and a wide array of other autoantibodies in 40 male and 40 female (and anticollagen antibodies in a 33-child subset of these) symptomatic children, both breast- and bottle-fed, referred by physicians, attorneys , or support groups. All children were born to mothers

with breast implants and averaged 6.8 years of age. A control group of 42 symptomatic children not exposed to maternal breast implants was also tested. Although there was a relationship of antibodies to symptomatology, there was no significant difference between the control and the experimental groups (Levine et al., 1996). As noted earlier, there is a modest prevalence of antinuclear antibodies in women of childbearing age. With rare exceptions as above, this is not known to cause health problems in their infants or young children.

Shanklin et al. (1996a) and Smalley et al. (1996a) have reported studies of children born to women with silicone breast implants. Shanklin et al. reported that 127 children born to women before placement of breast implants were in better health than 93 children born after implantation. The committee noted that this study population was very probably highly selected. There was no information to confirm the specific health status of these children. T-lymphocyte mitogen tests were reported in a summary fashion to be positive in 84% of a group of 33 children born after implantation. Stimulation indexes, that is, T-cell responses on exposure to silica, were also reported as overall average values in mothers and children (Shanklin et al., 1996a). Smalley et al. (1996a) reported that children of women with silicone breast implants had a proliferative response to silica. These authors used a stimulation index that compares the reaction of cells stimulated by the antigen (in this case silicon dioxide) with the reaction of unstimulated control cells. The mean stimulation index of 15 mothers was 182, whereas that of their 24 children was 77, in comparison to an index of less than 25 in historical normal controls. Comparison of small numbers of children of mothers without implants to children of mothers with implants suggested that the latter group had a higher mean stimulation index. Smalley et al. (1996a) concluded that silicone crosses the placenta, causing T-cell responsiveness to silica in the children. As noted earlier, these children were often not in good health.

These experimental procedures have been used in a number of reports from this group. In general, they are incompletely reported. Culture conditions, cell density, and the amount of particulate silica added to the cultures are not described. Nearly all data relate to colloidal silica, and there is insufficient or flawed evidence that this is a substance to which women with silicone implants are exposed. The stimulation indices are not interpretable without quantitative knowledge of the actual cellular reactions; comparative reaction counts may provide an index that is misleading if the actual counts are all below values that indicate a reliable test. It is possible that proliferative responses reflect some non-antigen-specific reaction to silica, but the authors' conclusion that silicone crosses the placenta and causes T-cell responsiveness to silica (an entirely different molecule) in children is speculative. In an independent assessment of

this test, Young (1996b) reported it to be unreliable and variable in ways that had no relationship to clinical facts or to the silicone breast implant status of the tested women. The studies reviewed here do not provide any evidence to alter conclusions on immunological effects reached earlier in the discussion of case reports.

Epidemiological Studies

Files of the Danish National Registry of Patients were used to identify all children born from 1977 to 1992 to a cohort of 1,135 women with cosmetic breast implants and to a comparison cohort of 7,071 women who had undergone breast reduction surgery. Cause-specific hospitalization rates among children, related to those of the general population, were calculated from this registry. Children were followed for the occurrence of adverse health outcomes from the time of birth to death, emigration, or until December 31, 1993. Adverse outcomes included most esophageal disorders, defined connective tissue disease, other rheumatic conditions, and congenital malformations. Findings among the 939 children of mothers with breast implants included higher numbers of esophageal disorders, but the excess was similar for children born before and after implantation. More frequent hospitalizations than expected for these conditions were also observed among 3,906 children of women who underwent breast reduction surgery. No significant increases in connective tissue diseases or congenital malformations were observed in either the breast implant or the breast reduction cohorts. Specifically, the investigators found four cases of esophageal disorders among children born after the mother's breast implantation, compared with 1.4 expected. However, the increased risk observed among children potentially exposed to silicone was similar to the excess risk found in silicone-unexposed children (12 cases observed, 4.5 expected). A slight, nonsignificantly increased risk of congenital malformation among children born after the date of the mother's implant was seen (21 cases observed, 15.9 cases expected), but was also found in the group of children born before implantation (59 cases observed, 49.4 cases expected). No cases of defined connective tissue disease or other rheumatic conditions were observed in children of mothers with breast implants, but the expected numbers were small and thus the power to detect an association was low.

The observed excess of hospitalization in Denmark for minor esophageal disorders among children of mothers with breast implants or breast reduction surgery suggests a lower threshold for seeking professional medical care for infant-feeding problems normally solved outside the hospital system. The absence of defined connective tissue disease or other rheumatic conditions in these 279 children suggests that the incidence of

connective tissue diseases is not likely to be greatly elevated in children of women with implants (Kjoller et al., 1998).

Since study participants were drawn from a nationwide register of patients and children were traced through population registers, sample selection bias was unlikely. However, using hospital record data, rather than clinical data collected prospectively, may limit the interpretation of study results. Episodic symptoms of dysphagia, feeding problems, abdominal pain, or vomiting are probably evaluated outside the hospital setting and escape recognition by the national registry. The average time of five years between the date of implantation and the birth of a child may be too short to appropriately evaluate the effect of implant gel fluid diffusion or rupture. Few data were available on breast-feeding history, and the type of breast implant was not specified in 16% of the sample. Nevertheless this study has moderately large numbers of women and children and is well designed.

CONCLUSIONS

The committee concludes on the basis of the studies reviewed in this chapter that evidence for an association of maternal silicone breast implants and children's health effects is insufficient or flawed. No biologically plausible causation has been suggested. Convincing evidence is available that silicon concentrations in breast milk are the same in mothers with and without breast implants, and thus there are no data to support transmission of silicone to infants in breast milk of mothers with implants. A modest number of normal mothers are positive for ANAs. Except for rare instances, as noted, evidence that this or similar situations in mothers with silicone breast implants have deleterious effects on children is lacking. Evidence for children's esophageal disease caused by maternal breast implants is insufficient or flawed.