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Safety & imaging of modern silicone breast implants

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SUMMARY

The studies described in this thesis derived from the recall of silicone breast implants of the French manufacturer Poly Implant Prothèse (PIP) from the European market in 2010. This was after it became clear that this manufacturer used unauthorized silicone gel and substandard manufacturing processes. Last December the director was convicted of fraud. Although the Dutch Health Care Inspectorate (IGZ) already asked all clinics and hospitals to recall women with PIP implants in 2010, it wasn't until a year later that it became known to the general public. In December 2011 the IGZ followed the French example and changed their advice to explantation of all PIP implants, regardless of whether they proved to be ruptured or not. From the 1990's to 2006 around 400.000 PIP silicone breast implants were sold worldwide, which affected approximately 3.000 women in the Netherlands.

Silicone gel filled breast implants have undergone vast changes in design, form and consistency since their introduction to the market in 1962. Although silicone breast implants were taken off the US market and were only allowed to be used in clinical trials from 1992 to 2006, in Europe they have been used throughout. Therefore most clinical experience and expertise in the use of implants was gained here. Silicone breast implants are used in a minority of cases (20%) for replacement of breast tissue after mastectomy and in a majority of cases (80%) for augmentation. Cosmetic surgery is a growing market worldwide and the regulation of medical devices such as silicone breast implants is different in Europe compared to the US or anywhere else in the world. The most important adverse effect of the use of silicone breast implants is the need for reoperations due to local complications such as capsular contracture, rupture, gel bleed, hemorrhage or infection, further described in **Chapter 1**. Nowadays it is widely accepted that women who will get silicone breast implants at a young age need to realize that most likely they will face repeated replacement of these implants.

Systemic complications such as lymphadenopathy have been described in women with silicone breast implants. In general, large studies did not show evidence of an association between silicone breast implants and cancer. There is however debate in literature on the influence implants might have on detection of very early stages of breast cancer. Furthermore, an association was found between breast implants in general and the development of a very rare form of lymphoma (ALCL) in capsular tissue surrounding implants. Studies on women with silicone breast implants have reported vague complaints such as fatigue and arthralgia, and at times also an association with proven autoimmune diseases. However, in large epidemiologic studies such association could never be proven, nor totally denied, due to the fact that these complaints and diseases are only prevalent in a very small group.

In the past two years the negative publicity about the PIP scandal caused unrest among women with silicone breast implants. Moreover, in medical literature a lot of articles were published on the subject in 2012. It is not the first time that silicone breast implants and the public opinion have

been frequent news items while at the same time there was a growing interest in performing research on complications. In **Chapter 2** the authors described a historical review on medical publications about silicone breast implants since their introduction to the market. The chapter gives insight into the subtopics which were popular in medical literature at certain points in time. The authors illustrated in a graph the number of articles per year correlated to news facts in the regulation history of silicone breast implants. This study shows that the popularity spikes in medical literature correspond with and follow shortly after headlines in leading newspapers such as The New York Times or the Daily Mail. Lay media influences medical literature and vice versa. This was also true when the French media linked the death of a woman with ALCL to the recall of PIP silicone breast implants and many women feared health risks. Media attention and this anxiety can also have an effect on research on complaints and health risks by introducing recall bias.

The studies described in this thesis on complaints in women with PIP implants were performed before December 2011, therefore providing a realistic view of the symptoms. The study described in **Chapter 3** is an example of a study that resulted from the media attention and the fact that women with unexplained systemic complaints, which they themselves thought to be associated with their silicone breast implants, felt ignored. At a special outpatient clinic, a joint collaboration of the Netherlands Association of Internal Medicine (NIV) and the Netherlands Society of Plastic Surgery, Hand Surgery, Aesthetic and Reconstructive Surgery (NVPC), these women were seen and examined by experienced consultants. These women had silicone breast implants of different manufacturers, not just PIP implants. The authors found a pattern of complaints consisting of fatigue, myalgia, arthralgia, morning stiffness and neurasthenia in more than 65% of these women. Complaints often started many years after implantation. The observed pattern of symptoms was comparable to the earlier reported 'autoimmune syndrome induced by adjuvants' (ASIA) in all women. An interesting observation was that in 69% of the women, explantation of the implants reduced their symptoms. In 80% of the women in our study women suffered both local and systemic complications, such as pain or capsular contracture. This last fact and the observation that 75% of the women had pre-existent allergies, might indicate that a small group of genetically predisposed women with a possible allergic constitution is more prone to develop both local and systemic complications. This relationship as well as possible patient related predictive factors are subjects of the authors' future research. The authors do advise their colleagues to consider examination and possible explanation of implants in women with serious systemic complications, even in the absence of local complications.

At the time the IGZ first requested clinics and hospitals to recall their patients with PIP implants, there were indications that PIP implants rupture more frequently than other modern silicone breast implants. However, the exact risk of rupture was unknown. The Medical Center Jan van Goyen was one of the first clinics in the Netherlands to follow the advice of the IGZ in the spring of 2011 and recalled all women that had received PIP implants. In **Chapter 4** the authors described the first prevalence rates of rupture in PIP implants and found that one in three women suffered from at least one ruptured implant. Of all 224 reviewed MRIs 24% of the PIP implants were found to be ruptured after a cumulative implantation time of 10 years. This rupture rate is comparable to

older generation implants, but probably more than twice to five times higher than the rupture rate in other modern breast implants. It is difficult to compare results as most recent studies on current brands available don't have the same cumulative implantation time. There seems to be no difference in implants from 2000 and 2001, despite the earlier advice of the IGZ to only explant the implants with lot numbers from 2001 onwards. Most women (70%) in our study reported no complaints during their visit to the plastic surgeon. Most of the ruptures were therefore asymptomatic intracapsular ruptures. The correspondence about the article is attached in the Addenda.

In **Chapter 5** the authors described whether clinical complaints of the examined women with PIP implants are related to the presence of rupture or not. No association was found between the most frequently mentioned local symptoms such as pain (18%), disfigurement (8%) or lumps (4%) and the presence of ruptures found by MRI screening. The frequency of complaints that women report is comparable to literature on other manufacturers of silicone breast implants. The fact that PIP implants rupture or bleed more often than others did not lead to more symptoms in the 112 women in this study. The only symptom and sign related to implant rupture was axillar lymphadenopathy. The physical examination by a plastic surgeon is not a reliable method to detect implant rupture, even MRI screening does not have 100% accuracy but is the best possible method available to diagnose implant rupture. The low specificity of 52% was in more than half of the cases caused by excessive gel bleed.

The IGZ changed its advice to explantation of all PIP implants after the women in our study were already included, which changed the design of our study after December 2011 to a prospective explantation study. In **Chapter 6** the explantation details of 214 removed implants were described. At explantation, 21% of the PIP implants turned out to be ruptured, a bit less than assumed at MRI screening. Due to the lack of large explantation studies of modern silicone implants, the results of this study contribute to the knowledge on the prevalence of silent ruptures. The sensitivity of MRI screening in this group of mainly asymptomatic women was 80% and the specificity 91%. In some countries women with silicone breast implants are advised to undergo frequent MRI screening (even every two to three years), according to the authors the accuracy of MRI screening in a day to day clinical setting does not justify this advice.

The disappointing accuracy of MRI screening to detect implant rupture, as described in Chapter 6, led to the development of a new and simple reporting or classification system. The Silicone Implant Reporting and Data System (SI-RADS) was developed by the authors and introduced in **Chapter 7**. As the old reporting system at times led to unclear and inconclusive MRI reports, we developed a simple system inspired by the Breast Imaging and Data System (BI-RADS), well known in breast oncology. The system describes two categories, A. the implant status and B. signs of extracapsular silicone leakage. For each category the radiologist needs to choose from four multiple choice answers, which represent a measure of confidence (e.g. intact, probably intact, probably ruptured and ruptured). A system like this is easily implemented in the daily practice and

can improve communication between radiologist and plastic surgeon and possibly even improve accuracy of MRI studies in diagnosing rupture in silicone breast implants.

The SI-RADS method was used in the study described in **Chapter 8** on the consistency of the accuracy of MRI screening to detect implant rupture in modern silicone breast implants. Two radiologists independently evaluated all MRIs of the 214 explanted PIP implants without knowledge of the first MRI report or the state of the prostheses at explantation. An improved sensibility and sensitivity of 93% was found and in most cases the radiologists agreed on the diagnosis. The interobserver variability was excellent with a kappa value of 0.92. Also the intraobserver agreement was found to be valid, two years after the first evaluation round. MRI screening proved to be a consistent method to diagnose rupture in modern silicone breast implants.

In **Chapter 9** the above mentioned results are compared to other medical literature on silicone breast implants, and PIP implants in particular. The prevalence of rupture of 21% in PIP implants found in our studies is in line with the results of other study groups in Europe. There is a need for better comparison and thus a need for well-planned prospective studies on the frequency of rupture in other silicone breast implants available on the market today. In order to change the public opinion and general view on the subject positively well-designed research on complications and safety of silicone breast implants as well as research on possible causal factors of complications is needed. Reliable and solid regulation and registration systems are paramount. Most importantly, women with local or systemic complications need to feel that they get the best possible treatment. I hope this thesis will place the recent PIP recall in the light of evidence based medicine instead of media hype.