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Maijers, M.C.

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CHAPTER 9

General Discussion
& Future Perspectives



GENERAL DISCUSSION

SAFETY

The main aim of this thesis was to collect relevant data on the complications and health implications of the recalled silicone breast implants of the French manufacturer Poly Implant Prothèse (PIP). What does the fact that they had been implanted with non-medical silicone gel filled prostheses mean to the at least 3000 affected women in the Netherlands? As outlined in this thesis' introduction, the alarming high number of reported ruptures in implants was the main concern addressed by the French health authorities, when they announced the first recall advice of the PIP implants in 2010.¹ In literature, some authors already questioned the quality of PIP implants² but no study had reported on the prevalence of rupture in PIP implants, which kick started our research. The prevalence of rupture and how this relates to the prevalence of rupture in other modern silicone breast implants is of utmost importance to judge on their safety.

PREVALENCE OF RUPTURE

In the Medical Center Jan van Goyen, a private clinic in Amsterdam, PIP implants were used frequently for breast augmentation in the years 2000 and 2001. The management of the clinic obliged to the request of the Dutch government to recall their patients from those years. The 112 women included in our study were the first ones to report to the clinic on our request for follow-up. However, to date more than 200 women have been seen by a plastic surgeon at this clinic and have been operated. The 10 year cumulative prevalence of rupture found in our first study was 24% per PIP implant, which affected one third of the studied women.³ In our first study, rupture prevalence was based on MRI diagnosis of rupture.³ In our follow-up study this 10 year cumulative rupture prevalence was adjusted to 21% per implant, which affected 27% of the studied women at explantation.⁴ Since our first publication, more colleagues⁴ shared their experience with PIP silicone breast implants and rupture prevalence.⁵⁻¹⁴ Table 1 shows our findings to be in line with all other literature to date on the prevalence of rupture in PIP silicone breast implants, based on diagnosis at explantation.

Table 1. Literature on prevalence of rupture in PIP implants, based on diagnosis at explantation

Name	No women	No implants	Follow up (years)	No explanted implants	% of women affected with rupture	10 year cumulative prevalence of rupture per implant
Maijers ⁴	112	224	10	214 (96%)	27%	21%
Berry ^{5,6}	460	920	7-12	326 (35%)	22.7-38.4%	19-40*
Quaba ¹³	484	968	1-13	676 (70%)	35.2%	ns (21.3% after 7.8 year)
Chummun ⁸	44	88	7	78 (89%)	ns	ns (21.8% after 7 years)
Crouzet ⁹	116	128	1,8	76 (59%)	ns	ns (3.9% after 1.8 years)
Carrillon ⁷	31	33	1,3	8 (24%)	ns	ns (37.5% after 1,3 years)

*ns = non specified, * estimates by Kaplan-Meier analysis*

What does this cumulative prevalence of rupture of 21% after 10 years say about the durability of PIP implants in comparison with other modern silicone breast implants available on today's market? As mentioned in the introduction, 10 year follow up data on 4th and 5th generation implants are yet to be published. The FDA published the Kaplan-Meier estimates of 10 and 8 year cumulative MRI diagnosed ruptures to be 10.1% in Allergan® implants and 13.6% in Mentor® implants for women after primary augmentation.¹⁵ Implant rupture rates are much higher for revisions or patients who underwent reconstructive breast surgery with implants.¹⁵ The Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) concluded in their report on the potential risks of PIP implants that PIP implants rupture more often than the 10-15% expected in 3rd generation implants.¹⁶ The few women with other implants we saw in our own study, because they underwent MRI screening before their implantation records were found that showed them to be implanted with McGhan® implants, had a cumulative 10 year prevalence of rupture of 5%.³ The previous estimates indicate that PIP implants will rupture at least twice as often as other implants on the market or even much more if new data in the future on modern silicone breast implants will prove implants to rupture in less than 5% after 10 years of implantation time.

As mentioned before in the introduction, research on prevalence of rupture or rupture rate is complicated.¹⁷⁻¹⁹ Not only because at the time of publication of ten year results, new types, new generations and even new manufacturers have entered the market and today's operation theatre, but also because asymptomatic women with implants might not always be motivated to come for follow-up and MRI screening. The fact that the letter that was sent to them explained that they were recalled on advice of the national government because of safety concerns, did help in our response rate. Most data on prevalence of rupture or other complications of silicone breast implants are studies financed by manufacturers.²⁰⁻²³ Unfortunately, most of these studies suffer from huge loss to follow-up of at times up to 79%-95%.²⁴⁻²⁶ Only a few large independent studies were organized in Scandinavia^{27,28} and the US.²⁹ The use of strict uniform protocols on how to calculate rupture rate and how to define rupture status are recently suggested to prevent current difficulties in comparing research outcomes of different manufacturers.¹⁹ For better data on long-term rupture rates of manufacturers still on the market today, large prospective multicenter studies should be conducted with a follow-up of at least 10 years. Manufacturers and independent researchers might need to work together by continuing post market monitoring, evaluation and international registration to produce evidence based proof on the durability of today's silicone breast implants.

CLINICAL CONSEQUENCES

With a prevalence of rupture at least twice as high as other silicone implants, what exactly are the health risks those 3.000 women with PIP implants in the Netherlands face? Both the NHS as the SCENIHR concluded quite recently that although PIP implants are more likely to rupture, they do not seem to cause any additional symptoms or health risks.^{30,31} The SCENIHR also stated that increased rupture or local inflammation in women with PIP implants is not associated with (breast)

cancer or specifically ALCL.²⁷ Among the 130 cases of ALCL³²⁻³⁵ worldwide 4 patients had received PIP implants and ALCL was lethal in 1 case. It was concluded from these data that this is of no statistical relevance.²⁷

Three to five times more clinical signs, especially increased loco-regional spread of silicone and lymphadenopathy up to 29.4% have been reported in recipients of PIP implants compared to other implants by some authors.^{13,31} Unfortunately, most large published studies on PIP implants up to date reported on rupture rate only and did not include clinical consequences or symptoms.^{13,36}

Asymptomatic rupture & management

Most women (70%) in our PIP studies reported no clinical symptoms or complaints and most of the time the silicone was kept in place by a fibrous capsule.³⁷ The clinical consequences of these asymptomatic and intracapsular ruptures remain frequently debated.³⁸⁻⁴¹ In our study, symptoms such as chronic pain, changed form and capsular contracture were not correlated with implant rupture. Lymphadenopathy was the only clinical sign, directly related to implant rupture and silicone leakage,³⁷ which was confirmed by others studying PIP implants¹³ as well as other manufacturers. If implant rupture does not lead to symptoms or signs, would a replacement operation not lead to unnecessary morbidity? Authors have questioned before whether asymptomatic women should indeed be explanted and receive new implants.^{38,42} Looking at health risks, the need for repeated revision/implant replacement surgeries are nowadays the most frequently mentioned complication or adverse effect after cosmetic breast augmentation surgery.⁴³⁻⁴⁵ An unnecessary health risk, one should avoid when possible.

On the other hand, one could argue that 30% of the women in our PIP study did mention some complaints, which they felt were acceptable enough not to seek medical attention for them.³⁷ The women in our study were healthy women who underwent cosmetic augmentation of healthy breasts more than 10 years prior to their recall. Apparently not all women return to their clinic with local complaints.⁴⁶ Eighteen percent of women experienced pain or a burning sensation and we found severe capsular contraction in 7.1% of the studied women. These complaints were not severe enough to report to the plastic surgeon, so he or she would have been unaware of these symptoms had there not been a recall.³⁷

Furthermore, we don't know the time of rupture in our study. Some women might have had ruptured implants for a long time, but it is reasonable to assume that most ruptures in our cohort happened quite recently, as most literature suggest chances of rupture to increase greatly after 7 to 10 years of implantation time.^{41,47} It might be too early now to conclude that implant rupture in these women doesn't lead to local or systemic complaints on the long run. Especially because we found in the descriptive study of women with silicone breast implants (of all kind of

manufacturers, including PIP) and systemic complaints, that their symptoms often started many years, up to 14 years, after their first implantation.⁴⁸

Taking into account the probably very low prevalence of systemic complaints and the results of our studies on PIP implants, we would agree with the European advice to replace non-PIP modern silicone breast implants only when they cause symptoms.³¹ One should bear in mind that intracapsular ruptures, which most often are 'silent' ruptures, even though they don't cause complaints now, do have a chance to cause extracapsular silicone leakage and complaints in the future.³⁸ It is therefore important to follow-up patients after breast augmentation every 5 years or strongly advice women to return in case of symptoms, both local and/or systemic. Plastic surgeons need to explain that most implants will rupture after 10 to 15 years and that women after breast augmentation most likely need more (sometimes up to five) revision and replacement operations during the course of their lives. In the case of PIP implants and their non-medical silicone gel, too many questions remain unanswered. Therefore, although most women in our studies had no complaints even in case of rupture, we would still advice to replace all PIP implants of all fabrication years with authorized new ones. In case of manufacturer errors in a car, the car model is recalled to prevent accidents in the future, not because it doesn't drive or is dangerous at the time of recall.

Symptomatic ruptures & management

If we say asymptomatic rupture in modern non-PIP implants are safe to be left in situ, when do we consider our patients symptomatic? Frequently described symptoms or complications of silicone breast implants are capsular contracture, hematoma, infections, rupture, gelbleed, changed form and pain⁴⁹⁻⁵¹. These local complications can also lead to systemic complaints of which lymphadenopathy and granuloma formation are the most well-known, especially in PIP implants⁵². Other systemic complaints or associations with systemic diseases such as autoimmune diseases or cancer are described in women with silicone breast implants,^{53,54} but a direct association has never been proved nor totally rejected^{55,56}. In PIP implants a higher frequency of rupture and gelbleed might according to some authors have led to more loco-regional spread of silicone and lymphadenopathy or cutaneous lesions and allergic dermatitis,^{52,57-59} we did not find proof for this in our studies, but did show examples of "milky intracapsular fluid," "excessive gelbleed" and changed color and consistency of even intact explanted implants.^{3,37} Per-implant exudate like in our study was also seen by others,^{5,58} but the exact clinical consequence remains unclear.

In chapter 3 we described a pattern of symptoms in women who blame their silicone breast implants for their sometimes vague, but at times incapacitating systemic complaints such as fatigue, arthralgia, muscle pain, neurasthenia, morning stiffness and cognitive problems.⁴⁸ Other authors have described women with systemic complaints and implant rupture to benefit from implant explantation and also in our study a significant number of women reported recovery from their complaints after explantation.⁶⁰⁻⁶² In literature on management of implant rupture in

symptomatic women we currently only address women with local complaints or signs. Women with silicone breast implants who present primarily with systemic complaints are often not seen by a plastic surgeon, as we don't feel complaints might be related to their silicone breast implants. A noteworthy finding in chapter 3 is that 80% of women who blamed their implants for systemic complaints also had local complaints when examined closely.

Of these 80 women, 51% reported chronic breast pain, 50% had severe capsular contracture and 35% had lymphadenopathy.⁴⁸ Most women (90%) in this study were women who had their implants for cosmetic reasons, just like the healthy women in our PIP studies.³⁷ Even though most women in our study would classify as symptomatic, because of their local symptoms, some wouldn't have been offered explanation or revision surgery because they only experienced systemic symptoms. This seems unjustified as also the ones without local complaints saw their systemic symptoms improve after surgery.

We recommend replacing all implants in symptomatic women with ruptured modern silicone breast implants (PIP or not). Furthermore, we would advise surgeons to examine patients who primarily present with systemic complaints closely for additional local complaints and consider MRI screening for rupture. In case of rupture in women with serious systemic complaints, without an adequate alternative explanation after thorough investigation, one might want to offer revision or explanation surgery, even without the presence of local complications.

IMAGING

If we agree to replace or explant ruptured silicone breast implants that cause serious systematic or local complications, the correct diagnosis of implant rupture is of crucial importance. Although some have argued ultrasound to be a cost effective alternative, MRI is widely acknowledged as the best imaging modality to diagnose intra- and extracapsular silicone implant rupture.⁶³⁻⁶⁷ Improvements in imaging protocols might lead to even more advanced silicone-specific imaging techniques.⁶⁸ Physical examination unfortunately has shown to be of little added value to diagnose implant rupture in modern silicone breast implants, which was also true in our study for women with PIP implants.³⁷ Still we would advise to perform physical examination, with special attention for local lymphadenopathy as this was found more often after implant rupture.³⁷

MRI SCREENING

The validation of MRI screening to diagnose implant rupture was often performed in studies on symptomatic women with a large variety of different types of silicone breast implants from different manufacturers and generations, often with huge variations in implantation time. Our studies were unique by the fact that, due to the recall, we were able to study sensitivity and specificity of MRI screening in a large cohort of non-selected, mostly asymptomatic women with a

single type, single manufacturer, single generation modern silicone implant, all after an implantation time of 10 years. Another important aspect of the MRI studies described in this thesis is the fact that the results of the MRI could be validated by the state of the implant at explantation, which is the best conceivable reference standard. This was also true for the women who had MRI intact implants and no complaints, which are a group of women who would not, outside the unique setting of this recall, ever have been operated.

Our MRI studies were done in two phases. In 2011, all MRI's were reported by one of three radiologists without the use of a structured evaluation and reporting system.⁴ MRI reports were compared to explantation results to evaluate accuracy in a day to day clinical setting. In 2013 all images were evaluated again by two of the three original radiologists following a newly designed interpretation and reporting system with the aim to determine accuracy and consistency of MRI results when compared to explantation results. Our study is until this day the only one evaluating inter- and intraobserver variability of MRI screening in modern silicone breast implants. The intraobserver variability could be evaluated because two radiologists reviewed the same MR images after two years. The consistency of accuracy is very important in the light of recommendations for MRI screening promoted by the FDA since the reintroduction of silicone breast implants to the US market,⁶⁹ which is under current discussion in several countries.⁷⁰

Although MRI proved to be a robust and valid screening method to diagnose both intra- and extracapsular ruptures in modern silicone breast recipients,⁴ we would still advise to use this radiologic tool in symptomatic women only. As we believe asymptomatic rupture would not have any management consequences, except perhaps for more frequent follow-up visits. Therefore, routine screening as the FDA recommends will lead to unnecessary high health care costs and morbidity. Even at the re-evaluation of all MR images in 2013 in consensus by two experienced radiologists, 12 of the 52 on MRI diagnosed ruptured implants were found to be false-positive MRI results. These women would have been operated on while having intact implants, although in half of these cases the surgeon did report excessive gel bleed at the time of explantation. In 3 cases (of which 2 were explanted in another clinic) one can argue that the operation report was unclear and the other 3 had a keyhole sign and did also in retrospect look ruptured, but were found intact at explantation. Some of these explanations for false-positive MRI results have been previously described in older generation implants.^{63,67,71} It seems from our studies that radiologic differentiation between excessive gelbleed and intracapsular rupture can be difficult in modern high cohesive silicone breast implants. There is no consensus in literature on the management of excessive gelbleed and since chances are they will be mistaken for intracapsular rupture, we suggest treating them equally and to explant or replace implants in symptomatic women only.

In our studies MRI screening not only prove to be a valid, adequate and robust imaging modality to diagnose implants rupture, but also proved to have a low intra- and interobserver variability. Still we showed the accuracy in a day-to-day setting to be lower than in a setting of MR images being read by more independent readers. The accuracy of MRI screening can even be improved by the usage of a simple, uniform and structured protocol, like the SI-RADS categorisation.⁷² We

would recommend the implementation of such a uniform categorization system, to improve communication between plastic surgeons and radiologists. Nevertheless, even with the use of such a strategy, still the sensitivity and specificity will be around 93% and not higher. For future MRI validation studies it would be useful to not only use a uniform reporting method for the radiologist, but also for the plastic surgeons to use a protocolled way of reporting explantation results. The definition of true rupture and gelbleed needs to be clearly stated and uniformly used to make results of future research on the safety and imaging of modern silicone breast implants better comparable to each other.

OTHER IMAGING MODALITIES

In the UK two large studies have investigated the use of ultrasound (USS) in PIP implant recipients and found high sensitivity of 91% to 97.3% and specificity of 93.1 to 96%, comparable to the accuracy of MRI.^{6,13} As it is suggested that the PIP implants manufactured after 2003 might be composed of a more liquid silicone gel, this might explain the higher accuracy of implant rupture diagnosis by USS found in PIP implants⁷³ than in other modern moderate to high cohesive silicone breast implants. On the other hand, gelbleed, which seems to be more frequently reported in PIP implants than others, is difficult to detect with USS.⁷⁴ Future research is needed to explore USS in other modern implants as a cheaper alternative to MRI screening.^{75,76} Other future innovations in implant rupture detection can be high-resolution ultrasound⁷⁷ or dual-energy CT.⁷⁸

PLACED IN PERSPECTIVE

What can we learn from the events that lead to the PIP recall and how can we assist not only those 3000 Dutch women with PIP implants, but also all other present and future silicone breast implant recipients? In our studies we found the health risk of PIP implant recipients to be comparable to complication risks of implants from other manufacturers. In line with this, the SCENIHR stated there to be no reliable evidence that ruptured PIP implants create a greater health risk than a ruptured silicone breast implant from another manufacturer, but at the same time stated that failure rates of non-PIP implants are not well documented in literature.³¹ Thus, we can start with providing evidence by conducting large scale prospective studies on safety of modern silicone breast implants, using uniform criteria to calculate failure rates.¹⁹ The future of silicone breast implants is difficult to predict. More research is needed on both local and systemic complications and on ways to prevent them. Manufacturing processes are changing and innovations in design and materials can for sure contribute to a reduction of complications.²⁸ The vast majority of women who have silicone breast implants have no systemic complications and therefore silicone breast implants will continue to have an important place in reconstruction after breast cancer and in breast augmentation. Still, up to 30% of women with silicone breast implants experience local symptoms, probably less than 0.05% incapacitating systemic symptoms and almost all women will need more revision and replacement surgeries in their lifetime. It is very important that manufacturers, plastic surgeons and researchers work together in the development of a safe product.

IDEAS FOR FUTURE RESEARCH

As explained already, we noticed more local complaints (in 80% of women) than expected in the study mentioned in chapter 3 on women with systemic complaints. A link between silicone related local and systemic complaints has been suggested before in literature.^{79,80} From our results one could suggest that silicone from either the silicone fluid or the silicone shell of the implant might trigger local immune responses that have an effect systemically and can therefore mimic autoimmune diseases. Another explanation for our findings could be that a small minority of women are predisposed to develop complaints of extreme fibrosis of the capsule locally and the pattern of complaints systemically. Authors have found HLA typing to be different in women with silicone breast implants and systemic complaints compared to women without these complaints.⁸¹

These predisposed women might also more frequently develop allergies.⁴⁸ The large majority of women tolerate silicone breast implants without any problems,⁸² locally or systemically, only a few have been described to be more prone to develop complaints.⁸³ In future studies HLA typing or immune serology (e.g. IgE) should be evaluated in these women as well as in healthy women. Such research could in the future help to identify women, who have the risk of developing more serious

complications from silicone breast implants. These women could for example be advised to use autologous tissue for breast augmentation or reconstruction. Our study does not support any routine allergy testing of women before silicone breast implant surgery as was suggested by the Health Care Inspectorate (IGZ), but we do recommend to explore what specific tests might have a role preoperatively in the future.

Future research should also aim to explain the immunologic pathways of local complications or immune serological alterations in local fibrous tissue of the capsule surrounding silicone breast implants *in vivo*. By studying these local immunological effects in women with extreme capsular contracture, we might find an explanation for systemic effects as well as innovative ways to prevent complications from silicone breast implants and improve biocompatibility.⁸⁴⁻⁸⁹

REGULATION

How was it possible that in Europe, fraudulent silicone breast implants of a certain manufacturer were banned so late from the market, while they were never approved on the US market and other type of implants from the same manufacturer were withdrawn from their market years before that?⁹⁰ The regulation of silicone breast implants in Europe differs from the US, where the FDA as one organisation decides about the fate of companies who want their medical products on the market.²⁵ While in Europe CE marketing license of medical devices can be quite easily obtained by any European company in any certification bureau.^{91,92}

Already in 2005, French plastic surgeons concluded after the analyses of the different catalogues of 9 laboratories selling ten brands of mammary implants on the European market (including PIP) that the European standard EN 12180 provides too little technical and no clinical or biological information on which a choice according to the real quality of implants can be made.⁹³ The PIP recall proved that the role of government and health authorities is important to ensure safety and high quality manufacturing.^{25,94} The regulation of prostheses used in patients is under debate in Europe as the PIP recall led to a growing lobby for a more uniform, strict and transparent regulation, following the US example.^{52,90,92,95,55} Better regulation, with a clear responsibility of providing long-term evidence on safety, would benefit both plastic surgeons and patients.⁹⁶

REGISTRATION

What would be the place of the silicone breast implant recipient herself? A well-informed and consented patient herself would also have some responsibility and the right to make decisions concerning breast reconstruction or augmentation that suite her personal preferences. She is required to come forward whenever she has complaints she thinks might be related to her silicone breast implants. Prior to implantation, she should be aware of possible complications and be well-informed by her surgeon. Professionals, but also breast cancer patient organizations as well as women who had silicone breast implants and systemic complaints lobby for better general

information^{51,97} and we could improve the way this information is incorporated in the way we currently counsel patients preoperatively.³¹

During our studies a striking finding was that most patients were unaware of the type, generation or manufacturer of their silicone breast implants. Apparently, we keep better track on the guarantee receipt of a 10 year-old Personal Computer than on the characteristics of implanted parts in our own body. This not only illustrates the trust patients tend to have in their doctors and regulatory authorities, but this unawareness also shows the need for a national or preferably international registration systems, in which patient data are linked to the lot numbers and implantation details of their breast implants. There is a need for better reporting of breast implant failures, in particular of ruptures, through the mandatory vigilance reporting system to identify potential design problems earlier.³¹ This kind of registration system has failed in the past in the Netherlands and the PIP recall has reinitiated the implementation plans of a new registration system, based on an Australian example.

To ensure its long existence, longer than the previous one, a well-designed financial plan is paramount in which responsibility for the registration will be shared between the patient, the surgeon who implants the prostheses, the manufacturer and the health authorities. In Scandinavian countries a well-equipped registration system has shown to improve quality epidemiologic research on implant safety, imaging and design.⁹⁸ Some suggest these kind of registries should not only include silicone breast implants, and that properly funded and maintained national and regional device registries are needed.⁹⁰

MEDIA

In chapter 2 we described the impact that media had on the regulation history of silicone breast implants and how mass media attention in newspapers are followed by peaks in medical publications on certain subtopics. This was also true for the PIP recall, which generated ample new evidence on safety and imaging of modern silicone breast implants as well as a lot of discussion on regulation and registration of implants in lay media.⁹⁹ Some authors argued that recent media attention had beneficial effect in improving recall,⁶ although it is important to keep in mind that mass media coverage can also introduce bias, like recall bias among symptomatic women.¹⁰⁰

The timing of the announcement of the French minister of Health to advocate the removal of all PIP implants just after the announcement of the death of a woman with PIP implants from ALCL can be called unthoughtful. The way news is told however, is unfortunately not up to the announcer, but up to journalists and editors. During the studies described in this thesis we also experienced our own examples of this phenomenon, when headlines didn't cover the essence of our research. However, when there is a lack of evidence or when patients feel ignored, this is to be expected.⁹⁹

On the other hand, if we take responsibility, act proactive and are involved in the product we implant in our patient, we can have a positive effect in providing evidence to support or reject certain decisions that are taken in the heat of the moment. We experienced ourselves that researchers can in fact guide regulators, when the Health Care Inspectorate (IGZ) followed our advice to also explant PIP implants prior to 2001.¹⁰¹ We found the lot numbers from 2000 to rupture just as frequently as the ones from 2001, long before Jean Claude Mas admitted to the use of the unauthorized silicone gel in those implants. Furthermore, the fact that we found no increase in complaints or signs, following the implantation of the more frequently rupturing PIP implants, lead to new evidence based recommendations at European level.³¹

Although the safety of any product placed in a human body should be critically explored and repeatedly questioned, immense negative media attention, which the PIP recall generated about silicone breast implants in general, based on our studies, unjustified. We hope colleagues will be inspired to share the excellent outcomes and aesthetic results of breast implant reconstructive and breast augmentation surgery. We hope that this thesis will help to place the PIP recall in perspective of evidenced based medicine instead of media hype.

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