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Ministry of Health, Welfare and Sport

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report

Meeting	International meeting on breast implants
Meeting date and time	Thursday 4 July 2019
Meeting location	Pakhuis De Zwijger, Amsterdam
Present	
Absent	
Copy to	

Date
26 September 2019

Our reference

Introduction

On Thursday 4 July 2019, an international meeting on breast implants took place in Amsterdam. The meeting was initiated by the Dutch Minister of Medical Care and was organised by the Ministry of Health, Welfare and Sport in collaboration with the National Institute for Public Health and the Environment (RIVM). The meeting gave a diverse group of more than 100 stakeholders, including clinicians, academic researchers, regulators, policy makers, industrial experts and patients a platform to share knowledge about health complaints of women with breast implants. The aim was to provide an update on available information on health (side) effects and to discuss opportunities and plans for new research on breast implants and potential health effects. The meeting had an open atmosphere and the interaction between speakers and audience was animated and respectful.

Speakers and audience agreed that the following key elements should be addressed during the meeting:

- Which are the most important research questions concerning breast implants and potential health effects?
- Which methods and which data can be used to answer the questions?
    - Smart ways to use existing data.
    - Studies to generate new data.
    - How to involve patients in the research design.
- How can new insights be translated into clear and useful information for patients and for women considering to get breast implants?

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Opening of the meeting

At the start of the meeting, three different personal perspectives on benefits and risks of having breast implants were shown in a video. The meeting was then formally opened by the deputy director of the Pharmaceuticals and Medical Technology department Karla van Rooijen on behalf of the Dutch Minister of Medical Care, Bruno Bruins. The minister expressed his gratitude to the three women who were willing to share their experiences on video. These women showed the complexity of the discussion on breast implants. The meeting participants were asked to exchange knowledge on breast implants and related illnesses, to share opinions and ideas and to set an agenda for the future research together.

Morning programme 'Breast Implants and health (side) effects'

Breast Implant Illness by Jan Willem Cohen Tervaert

Overview of systemic symptoms in women with silicone breast implants

Jan Willem Cohen Tervaert elaborated on a set of symptoms reported to occur in women with silicone breast implants that has been described as breast implant illness (BII) or Autoimmune Syndrome Induced by Adjuvants (ASIA). Cohen Tervaert characterised BII/ASIA as presenting systemic symptoms with signs of immune activation, including fatigue, cognitive signs and joint and muscle pain. The prevalence of BII/ASIA is unknown and epidemiological studies on the link between breast implants and BII/ASIA remain inconclusive. Patients that meet the criteria for BII/ASIA often have pre-existent allergy, fibromyalgia and/or a pre-existent auto-immune disease. Cohen Tervaert quoted a review which calculated from literature data that explantation of breast implants resulted in 75% of the cases in improvement of symptoms. Cohen Tervaert concluded that breast implants are not safe and pleaded for more research to show which types of patients are at risk and to unravel the mechanism behind BII/ASIA.

Update FDA by Binita Ashar

Review of the FDA meeting of March 2019

In March, an open public meeting of the FDA Advisory Committee regarding the safety of breast implants took place. In this meeting, several topics on breast implant safety were discussed with a variety of national and international experts including patient groups. The patient perspective was central in these discussions. Ashar spoke about concerns such as Breast Implant Associated – Anaplastic Large Cell Lymphoma (BIA-ALCL) and the systemic symptoms some women with breast implants experience, referred to as breast implant illness (BII). She indicated that FDA's advisory panel recognises the need for data collection and registries and that the FDA is taking steps with regard to risk communication and evidence generation. These steps include labelling changes, such as a warning box, a patient decision list and incorporating ingredient information. Furthermore, Ashar declared that the FDA will continue to update the public on medical device reports on BIA-ALCL and in addition on medical device reports of the systemic symptoms referred to as BII. Taken together, the FDA believes their collective efforts will improve risk communication and evidence generation regarding the safety of breast implants.

Research The Netherlands by Carl Moons, Prabath Nanayakkara, Robert Verheij and René van der Hulst
Implant safety: reporting of side effects, use of existing data, patient characteristics
Carl Moons called for an improved system for evaluating and monitoring devices both before and after market access 'at the front and at the back'. At the front, the Health Innovation Initiative Holland (Hii Holland) is being launched. This is a nationwide infrastructure where all stakeholders are involved at the beginning of evidence generation, deciding together which evidence is desired for market access, clinical use and reimbursement of devices that will contribute to better and more sustainable care. At the back, the Dutch Implant Registry, and the Dutch Reporting Centre for Adverse Effects of Medical Implants (MEBI) enable the collection of more data about health effects and safety of implants. MEBI is an independent centre where both patients and health care providers can report health effects that may be related to an implant. The majority of reports the centre received until now were about breast implants. The top 5 of the reported symptoms were fatigue, arthralgia, breast pain, loss of personal independence in daily activities and memory impairment. MEBI has a unique value for research on safety of implants after market access. MEBI acts when adverse effects related to implants are e.g. unexpected, severe, or clustered in time or space. Moons emphasised that devices and implants must have health benefits and an acceptable benefit risk ratio.

René van der Hulst explained that for women with a reconstruction after breast cancer as well as for women who underwent breast augmentation, quality of life generally improves. However, he also indicated that plastic surgeons recognise potential disadvantages of breast implants. Plastic surgeons are involved in research on safety and performance of breast implants, and initiated the Dutch Breast Implant Registry (DBIR). Van der Hulst acknowledged that there are women with breast implants and systemic health problems. He pointed out, however, that these problems have only been studied in selective populations and that information about prevalence of serious side effects and risk factors, including patient characteristics, is lacking.

Robert Verheij presented opportunities for research to be performed by the Netherlands institute for health services research (NIVEL) in collaboration with DBIR, the Maastricht University and the RIVM. The proposed research uses the general practitioners' electronic health records as a continuous source of data combined with data from DBIR and Statistics Netherlands (CBS). This will enable evaluation of health complaints before and after implantation, and comparison of women with breast implants and complaints to relevant controls. The research aims are to find out which health problems women with breast implants have, and whether these can be related to the implants.

Prabath Nanayakkara runs an outpatient clinic for patients with symptoms that are suspected to be associated with breast implants. He evaluated approximately 800 patients since 2011. The clinic has a long waiting list. Nanayakkara reported that many questions about the health complaints in people with breast implants remain unanswered, such as the aetiology of

health (side) effecs in people with breast implants, the pattern of complaints, and patient related risk factors. The two main aims for the research that Prabath Nanayakkara proposed are to 1) develop a national protocol to determine indications for explantation, and 2) to identify markers that can predict who may develop health (side) effects. To do so, research should focus on substances or particles and on biochemical parameters that might serve as disease markers, and on patient factors (such as allergies) related to the health complaints.

Afternoon programme 'Opportunities: registries, definitions and data'

RIVM report on macro textured implants and BIA-ALCL by Riny Janssen

Riny Janssen presented the RIVM's interpretation of the recent French ban on macro-textured breast implants because of an increased risk of BIA-ALCL. She explained that the RIVM interpretation distinguishes Allergan Biocell implants from other implants banned by the French decision. The majority of BIA-ALCL cases have been found with Allergan Biocell implants, and it was deemed likely by RIVM that these implants are associated with an increased risk. On the other hand, Janssen indicated that RIVM judged it was not possible to substantiate scientifically whether other implants pose a similar risk as Biocell due to the small number of cases of BIA-ALCL, the limited use of these implants and lack of clarity about the definition of texturing. She emphasised that the availability of good registries and registration according to uniform definitions about e.g. texturing would have been very helpful in this interpretation and are necessary for future research on implant safety.

Characterisation of Breast Implant Surface Texture by Louise Mulroy

Louise Mulroy showed the plans of an International Working Group to propose a classification system for international agreement to categorise the surface texture of breast implants. She explained that a common classification system on surface textures of breast implants is essential to provide a framework for analysis and pooling of data, to facilitate communication between regulators, registries and manufacturers, and to improve information available to regulators. Mulroy showed that currently, there are a number of classification systems using different parameters and categories. She announced that the international working group now works towards a proposal for international agreement on one model.

Registries (DBIR, ICOBRA) by Marc Mureau.

Marc Mureau elaborated on the importance of the availability of good quality data from registries such as the Dutch Breast Implant Registry (DBIR) and the International Collaboration of Breast Registry Activities (ICOBRA). He stated that plastic surgeons have the responsibility to share data in order to do research on breast implant safety. Furthermore, he indicated that reliable and valid national data on breast implants are important to optimise traceability of patients for a recall, patient information and counselling in order to improve quality of care. According

to Mureau, data from DBIR can be merged and matched with other national registries such as the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA), NIVEL, and the Dutch Implant Registry. Mureau believes that international collaboration is pivotal to increase knowledge on very rare side-effects including BIA-ALCL.

Questions and discussion

During the meeting there was plenty of opportunity to ask questions and for discussion among the audience and the speakers. The questions and discussions are described below in a clustered manner. Some questions could be answered by the panel, others could only be debated or could not be answered at all.

Research questions that need to be investigated

A number of research questions regarding breast implants were identified, some of which were presented by speakers, while others came up during discussions. According to panel members or participants in the audience future research should/could focus on these questions. It is important to note that time did not permit prioritization of proposed research questions although this was considered to be an important issue. Proposed research questions and gaps in knowledge are:

- How can the systemic symptoms referred to as BII or ASIA be summarised into a uniform and generally accepted definition?
    - The description of BII/ASIA is symptom driven and includes that explantation of breast implants improves symptoms. In order to make optimal use of existing data and proceedings of research, definitions and symptoms should be predefined. This will help clinicians to decide when to act.
- What are possible disease markers for women with breast implants and systemic symptoms referred to as BII/ASIA that distinguish them from women with breast implants without these health complaints and from controls without breast implants?
    - Currently, disease markers, e.g. blood markers, for BII or ASIA are not available. Availability of such markers could provide valid information on which clinical decisions can be based, e.g. about treatment, or whether or not to explant a patient's implants.
- What is the incidence and/or prevalence of BII/ASIA?
    - This can only be answered after a uniform and generally accepted definition is available.
- For BII/ASIA pre-existent allergy or auto-immune disease are known to play a role; what is the mechanism behind this, and what is the role of other factors such as the type of breast implant used?
- Now that it is confirmed that the type of breast implant is involved in the development of BIA-ALCL, what is the contribution of genetic factors and patient characteristics such as pregnancy or smoking history on development of disease?

Research designs

The strengths and limitations of a number of possible research designs were discussed to meet the main research questions identified above. General comments about new research on breast implants were to be aware of important confounders such as smoking, and the difficulty to find a proper control group. Several study designs were proposed and discussed. Like the research questions, also study designs were not prioritized. Feasibility of designs was not discussed extensively. Proposed research designs were:

- A retrospective study in patients with and without breast reconstruction with implants using data from breast cancer registries.
    - The panel emphasised that breast cancer populations are different from patients that received breast implants for cosmetic reasons. Breast cancer patients received immunotherapy/chemotherapy which is a major confounding factor. Outcomes of studies using breast cancer registries may therefore not be valid for patients that received breast implants for cosmetic reasons (70% of patients).
- Large prospective studies can be performed to address systemic symptoms in women with breast implants.
    - Not all participants considered this to be a feasible scenario.
- It was proposed to assess genetic factors linked to the disease in patients diagnosed with BIA-ALCL.
- A cohort study in patients with systematic symptoms and breast implants could be used in order to search for a disease marker.
- Combining (existing) data from studies and registries such as NIVEL data and DBIR enables research on the health problems women with breast implants experience, and whether these can be related to the implants.
    - There are a lot of data out there already. It was therefore recommended to make an inventory of the data landscape in order to make better use of the information that is available. In line with that, it is important not to repeat every study in every country.
    - It was questioned whether the registries have been around long enough to answer all questions now. It may take a longer time for registries to contain all the necessary data.

Sharing data and resources: who should pay

- The issue of data sharing from registries with industry was raised. Vice versa, questions were asked about industry sharing data for public use.
- It was pointed out that existing data from registries could be used for post-market surveillance (PMS) by industry. In the audience it was then emphasised that although registries are very important, they do not replace PMS. Multiple sources of data should be used; manufacturers are always responsible for good quality PMS.
- A lack of manpower and resources may withhold clinicians and researchers from collecting data. There are several good quality registries in healthcare in the Netherlands. The discussion with all stakeholders is who needs to pay for these registries. According to

the panel, insurance companies, government and industry should all pay their share. Manufacturers are responsible for safety of their products. From the audience it was stated that, if industry pays, the patient pays. For this reason it was indicated there needs to be a role for the government.

Safety of breast implants
Part of the discussion concerned questions and uncertainties about product issues of breast implants. For example, information about the contents and properties of devices is not available for the general public, and it is unclear whether certain characteristics of the implants may cause problems.

- A specific question in the audience was why the ingredients and composition information are not made publicly available by the manufacturers of implantable devices. How could one ever decide if these products contained harmful, i.e. toxic or allergenic components for patients, or perform research on these topics?
- One attendee questioned why authorities allow prostheses to leak. In response, a panel member added that clinicians consider devices safe for use when they receive market authorisation.
- It was questioned whether silicones are the origin of the symptoms experienced by patients, as silicones are used in many other products including implants (e.g testicular implants).
- It was pointed out that there are alternatives for silicone breast implants, however, these may not have the same cosmetic result. Saline as filling of the implant is an alternative deemed safer in case of rupture, but the envelope remains silicone and may still lead to similar health issues. Other solutions mentioned for women missing a breast, include reconstruction with own tissue.
- It was advised to be careful with placing breast implants if there is a history of allergies and of auto—immune diseases.
- The observation was made that breast cancer patients are instructed to come for follow up, while cosmetic patients are not. It was proposed that also patients who received breast implants for cosmetic reasons should be seen at least every 5 years.
- One attendee asked why breast implants changed colour during their implantation period. A panel member replied that silicone implants trap certain biological substances. These are assumed to be responsible for the colour change.

Translation of available data and information to patients
The perspective of patients had a major role in the discussion. In the afternoon discussion a patient representative took part in the panel.

- It was emphasised that patients need honest and useful information about benefits and risks of breast implants and about whom to turn to for adequate care if they experience health complaints.
- An identified difficulty in the communication to patients that experience health problems is the absence of a defined disease. Not all patients experience the same complaints and some complaints overlap with other conditions. This makes diagnosis difficult.

- It was agreed that it is important to keep patients and patient organisations involved in the steps taken in research on potential health effects caused by breast implants.
- It was again indicated that information from industry, registries and research may need to be disclosed for patients. It was pointed out that the information for patients should be very clear.
    - The audience addressed transparency of manufacturers about breast implant ingredients. Although this kind of information is not available for the general public, it is for notified bodies. Information about ingredients is part of the technical file that manufacturers are required to put together, and is via this route also available for competent authorities. One of the panel members wondered whether it is an opportunity under the MDR, that ingredients can become part of the implant card or of EUDAMED.
    - It was brought up from the audience that there is limited information about degradation of implants inside the body, at least not publicly available.
- It was emphasised that patients need clear communication about risks and benefits, and a leaflet is not enough. It was explained that patients have a hard time understanding leaflets. Honest information about risks and benefits for patients was considered very important.

General strategies to enhance understanding of side effects of implants
A discussion took place on possibilities to use the same kinds of methods and study designs as discussed for breast implants also for other types of implants. This was considered to have great potential: make better use of existing data; combine real world data and clinical trials
At the end of the meeting the audience was asked to send additional input to a dedicated e-mail address. The chair informed the audience that all information given during and after the meeting will be collected to guide future research into health (side) effects of implants.