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Establishment of treatment methods without critical reflection

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New treatment methods are sometimes introduced with no knowledge of whether the method yields better results than established treatment or how frequently complications arise.

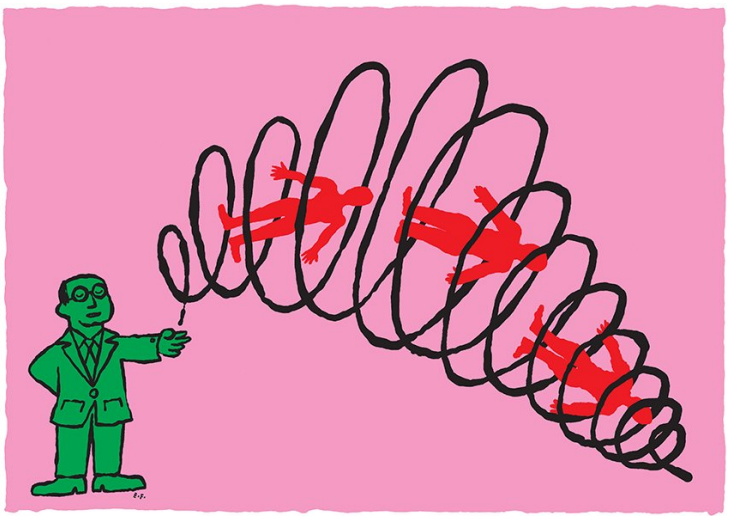

Illustration: Espen Friberg

In 2002, a new sterilisation method for women (Essure) became available, which was reported to be effective and result in few complications (1). As it turned out, the method caused far more, and more serious, complications than expected. In August 2020, a settlement was reached between the manufacturer and 39 000 women who had filed lawsuits. The manufacturer agreed to pay USD 1.6 billion to the women (2) but refused to acknowledge that the method had caused a large number of complications, many of them serious. The device has now been taken off the market.

These events illustrate the importance of critical reflection when introducing new treatment methods. They also show how crucial it is for the manufacturer, the hospital management and the attending doctors to be aware of their responsibilities. Below we discuss several aspects of this case.

The Essure implant

When it was introduced, the hysteroscopic sterilisation method known as Essure was regarded as a good alternative to the standard laparoscopic tubal ligation (1). The 4 cm Essure implant could be inserted into both fallopian tubes without anaesthesia by means of a hysteroscope. The implant consisted of two coils made of a nickel-titanium alloy and stainless steel, respectively, wrapped in polyethylene terephthalate (PET) fibres. After insertion, the device elicits an inflammatory response which, after a period of three months, permanently occludes the fallopian tubes. The implant was intended to remain in place throughout the woman's life.

Before its introduction on the market, the method, which was classified as an active implantable medical device (AIMD), was trialled in two observation studies with relatively few patients, and only a few women were monitored for more than one year (3).

Following the market launch, a large number of long-term complications were reported, especially to the US Food and Drug Administration (FDA) and the EU (4–6). In 2016, the FDA issued a 'black box warning', its strongest form of warning. In 2017, the EU decided to suspend its CE marking for Essure in light of the reported complications. Shortly after this, the manufacturer (Bayer) pulled the device from the market, except in the US, reportedly due to low sales.

The most common complications are pronounced pelvic and abdominal pain, heavy and protracted menstrual bleeding, headache, nickel allergy/hypersensitivity, fatigue, hair loss, perforation into the abdominal cavity and breakdown of the implant into fragments that are found in other parts of the body, including in the pulmonary circuit. Fatalities have been reported as well (2–7).

Documentation of new treatment methods

When new treatment methods are planned to be introduced into clinical practice, we believe two important questions should be asked: 1) Is the method effective and better than the standard method? and 2) Is the method safe, i.e., does not cause more complications than the standard method?

Randomised, controlled trials should be conducted to determine whether a new treatment method is better (more effective) than (a) previously used method(s). These trials can be carried out with stringent inclusion and exclusion criteria or as pragmatic trials (8). The first type of trial has a well-defined population and examines the efficacy under ideal conditions. The second type permits broader inclusion criteria and fewer exclusion criteria so that a larger segment of the relevant population is included (8). This provides information about the effectiveness that more accurately reflects typical clinical practice. No randomised, controlled trials were conducted on the Essure implant.

When new treatment methods are planned to be introduced into clinical practice, we believe two important questions should be asked: 1) Is the method effective and better than the standard method? and 2) Is the method safe?

Ideally, a pragmatic trial should have been carried out before the Essure implant was introduced. This would have hardly been possible in Norway, however, when the method was introduced in the early 2000s. At the time, limited capacity in Norwegian hospitals made it difficult to get a tubal ligation. The procedure was only prioritised in those few cases where there were medical grounds for sterilisation or the woman was undergoing surgery for other reasons.

Moreover, complications associated with a new treatment method are not always exposed in randomised, controlled trials. It is often the case that too few patients are included in the trials and the follow-up period is too short. This means it is even more important to establish registries in which all those using the new method can register their experiences on an ongoing basis.

In the case presented here, the trials conducted prior to market launch were small and of poor quality, and no registry was established either internationally or nationally (1, 3, 7). As a result, the complication rate, which was high and often serious, was discovered many years too late.

More than one million Essure implants have been sold internationally (9). A total of 15 % of the devices in the US and 16 % of those outside the US have been removed by laparoscopy/laparotomy because they could not be removed hysteroscopically (10). Exact information about the number of women with Essure implants in Norway is difficult to obtain, but the figure is likely to be several hundred (personal communication, Norwegian Patient Registry). There may be several thousand, but the codes used in the registry are unclear.

CE marking

It is our impression that many people, including health professionals, believe that CE marking of new medical equipment indicates that the product's efficacy and potential complications have been adequately documented.

In fact, CE marking means that the manufacturer has conducted a 'conformity assessment' – that is, it has documented that the product complies with the basic legal requirements regarding design, production method, labelling and instructions for use. In Norway, all medical equipment must be registered in the equipment registry before being placed on the market.

There is no government scheme for approving medical equipment, and CE marking is not a 'stamp of quality' from the authorities. This mark says nothing about the method's medical

efficacy and complication rate compared with established treatment. Accordingly, medical equipment, including implantable devices, is not required to meet the same documentation requirements as new medications.

It is crucial that incidents with medical equipment are reported

Manufacturers, health professionals and hospitals that adopt the use of new medical equipment have a responsibility vis-á-vis their patients to ensure that adequate documentation is available, and at a minimum that the results are registered on an ongoing basis. Unfortunately, there are many examples of implantable medical devices being used without adequate documentation of the efficacy and complications. Examples of this are pacemakers/heart starters with deficient technology, as well as vascular grafts, tracheal implants and pelvic mesh devices that have caused unacceptable complications (11–14).

Requirements of hospitals and doctors

Hospitals and doctors must meet stringent requirements when decisions are taken to use new treatment methods. The requirement of responsible conduct in section 4 of the Health Personnel Act and in section 2–2 of the Specialist Health Service Act is crucial in this regard. Any party that provides health and care services must ensure that the service works systematically to improve the quality of care and patient and user safety. For the hospitals, this requirement is set out in section 3–4 of the Specialist Health Service Act. It is also stipulated in the regulations on management and quality improvements in the health and care services, which include requirements of effective organisation, risk assessments, procedures for handling adverse incidents and systematic quality improvement efforts (15, 16). Other legal requirements are important to note as well, including the provisions on information and patient involvement in section 3 of the Patients' and Users' Rights Act and the duty to report adverse incidents, faults or deficiencies to the Norwegian Medicines Agency when medical equipment was, or may have been, involved (Medical Equipment Act, section 11).

Hospitals are required to have good routines for systematising and evaluating results following the introduction of new technology/implants, as well as for reporting complications and handling adverse incidents.

The boards of the health trusts have a general responsibility to ensure that the hospitals operate in accordance with and fulfils their obligations. This is set out in section 28 of the Health Authorities and Health Trusts Act. The board is responsible for ensuring that the hospital is organised and operated efficiently, and it is also required to conduct oversight of the operations. This includes, for example, ensuring that the health trust has adequate routines for introducing new methods and good routines for handling adverse incidents, evaluations and quality improvement.

Oversight and duty to report

The Norwegian Medicines Agency conducts oversight of products, distributors and manufacturers of medical equipment. This may result in an order to remedy faults or deficiencies and, in serious cases, to prohibit use of a device. Adverse incidents, faults or deficiencies involving or possibly involving medical equipment must be reported to the Norwegian Medicines Agency. An incident may be caused by a product failure, usage error or a combination of these. When the agency receives a report about an incident involving medical equipment, it assesses the risk and potential consequences for patients and any need for immediate measures. If the report comes from the health service and has not already been reported to the manufacturer, the agency ensures that the manufacturer is notified.

The Norwegian Medicines Agency follows up the manufacturer, which must report back about the follow-up and assessment of the incident, including measures to prevent a similar

incident from recurring. In our experience, the agency seldom provides information to the health service or to patients about the potential risk of adverse effects. According to the legislation, this responsibility rests primarily with the manufacturer or supplier of the medical equipment.

We can learn a great deal from the Essure case, and the introduction of this treatment method cannot be described as anything but scandalous

The Norwegian Medicines Agency has stated that it has received very few reports about the Essure implant. We know of several women who have had the implant removed due to adverse effects, but these cases have not been reported. It is important that doctors are aware of their duty to report and that hospitals have good reporting routines. This is crucial so that the agency, the manufacturer/supplier and the health service know about the possible adverse effects. At worst, many more people could be harmed if incidents are not reported.

Conclusion

When new medical equipment is sold and clinically implemented, the manufacturer and supplier, as well as the hospital's management and doctors, all bear a great responsibility. While the product must obtain a CE mark, the clinical efficacy compared with established standard treatment should be documented as well. If this is not done, the product should only be introduced as part of a scientific study, and the complication profile must be documented. It is crucial that incidents with medical equipment are reported. This is the only way that government authorities, the manufacturer, the health service and patients can know about adverse effects and other deficiencies. In the current situation, it seems totally random whether serious deficiencies are exposed and whether patients are informed about it.

We can learn a great deal from the Essure case, and the introduction of this treatment method cannot be described as anything but scandalous. It is essential that health professionals are aware of the potential complications of this sterilisation method so that patients who develop problems can receive causal and effective treatment.

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