Male inguinal hernia repair with mesh. Short- and long-term results and the question of infertility.

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Short- and long-term results and the question of infertility

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Male inguinal hernia repair with mesh. Short- and long-term results and the question of infertility.

Abstract

Background: In the nineties, the patients with inguinal hernias were exposed to several newly developed repair techniques using alloplastic mesh prosthesis. Although the scientific knowledge was limited, the new techniques were rapidly introduced due to surgical enthusiasm, but also by an eagerness to reduce the recurrence rate and to shorten the time to recovery. When the first study of this thesis was initiated there were almost no randomized controlled trials comparing the short- and long-term results of open tension free repair (Lichtenstein) and totally extraperitoneal laparoscopic repair (TEP).
The recurrence rates have since then been markedly reduced and the focus has moved towards studying other side effects of inguinal hernia surgery. The use of mesh in inguinal hernia surgery has been proposed to increase the incidence of male infertility due to inflammatory obstruction of the structures of the spermatic cord.
Aims: To compare the Lichtenstein and the TEP operation techniques regarding short- as well as long-term results. To assess the risk of male infertility following inguinal hernia mesh repair.
Methods: The first two publications were based on a prospective randomized controlled study comparing the the two repair techniques, with both short- and long-term follow-up. The next two publications were derived from the Swedish Hernia Register. One was a prospective study, comparing by questionnaire, involuntary childlessness after bilateral inguinal hernia repair with or without mesh. The other was a retrospective study comparing the expected and observed incidences of diagnosed male infertility after inguinal hernia repair with or without mesh.
Results: TEP resulted in less consumption of analgesics, shorter sick leave, faster recovery, longer operation time, higher hospital costs and less impaired inguinal sensibility. In the long-term both methods had a high patient satisfaction rate, almost no impact on day-to-day life and a low frequency of persistent severe chronic pain. Bilateral inguinal hernia mesh repairs in men did not increase the incidens of involuntary childlessness. Inguinal hernia mesh repairs were not associated with a clinically important increase of diagnosed male infertility.
Conclusions: TEP and Lichtenstein are comparable techniques which both have overall good short- and long-term results. Inguinal hernia mesh repair is a safe method regarding male infertility.

Key words: inguinal hernia, ‚groin hernia, hernia repair, Lichtenstein, TEP, mesh, male infertility

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To Ann, Emma and Olof

Contents

List of publications

This thesis is based on the following publications, which will be referred to in the text by their numerals.

1. Andersson B, Hallén M, Leveau P, Bergenfelz A, Westerdahl J. Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: A prospective randomized controlled trial. *Surgery. 2003 May; 133(5): 464-72.* PMID: 12773973 © 2003 Mosby, Inc. Reprinted with permission.

2. Hallén M, Bergenfelz A, Westerdahl J. Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial. *Surgery. 2008 Mar; 143(3): 313-7. Epub 2008 Jan 14.* PMID: 18291251 © 2008 Mosby, Inc. Reprinted with permission.

3. Hallén M, Sandblom G, Nordin P, Gunnarsson U, Kvist U, Westerdahl J. Male infertility after mesh hernia repair: A prospective study. *Surgery. 2011 Feb; 149(2): 179-84. Epub 2010 Jun 12.* PMID: 20542309 © 2011 Mosby, Inc. Reprinted with permission.

4. Hallén M, Westerdahl J, Nordin P, Gunnarsson U, Sandblom G. Mesh hernia repair and male infertility: A retrospective register study. *Surgery. 2012 Jan: 151(1): 94-8. Epub 2011 Sep 22.* PMID: 21943643© 2012 Mosby, Inc. Reprinted with permission

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Abbreviations

CLINTEC	Department of Clinical Science, Intervention and Technology
EHS	European Hernia Society
ICD	International Classification of Diseases
IEHS	International Endohernia Society
IKVL	Clinical Sciences Lund
IPOM	IntraPeritoneal Onlay Mesh
ns	Non significant
MD	Doctor of Medicine
MH	Magnus Hallén
PhD	Doctor of Philosophy (in Medical Science)
PMID	PubMed - indexed for MEDLINE
RCT	Randomized Controlled Trial
SD	Standard deviation
SHR	Swedish Hernia Register
TAPP	TransAbdominal PrePeritoneal repair
TEP	Totally ExtraPeritoneal repair

Thesis at a glance

Publication	Aim	Method	Results/Conclusions
Study 1 Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: A prospective randomized controlled trial.	To compare two mesh-based surgical techniques for inguinal hernia repair namely TEP and Lichtenstein.	Three surgeons performing both techniques in the 168 included patients. Follow-up with question-naire and clinical examination after one week, six weeks and one year. Independent observer.	TEP is associated with less postoperative pain, shorter recovery and sick leave, less hematomas, less impaired inguinal sensibility, longer operation time, higher hospital costs and more testicular pain.
Study 2 Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial.	To compare the long-term results of the two surgical repair techniques app-lied in study 1.	The same pati-ents as in study 1. Follow-up after minimum six years by ques-tionnaire (92%) and clinical examination (88%). Indepen-dent observer.	Equally good long- term results and low recurrence rates.TEP is associated with more chronic testicular pain but less impaired inguinal sensibility.
Study 3 Male infertility after mesh hernia repair: A prospective study.	To determine the prevalence of infertility, measu-red as involuntary childlessness, in men who had undergone bilateral inguinal hernia repair with and without mesh.	A questionnaire study from SHR. Men 18-55 years of age. Study group: 376 men operated with mesh. Two control groups: 186 men operated with-out mesh and 386 men from the Swedish population.	Bilateral inguinal hernia mesh repair do not increase the frequency of involuntary childlessness.
Study 4 Mesh hernia repair and male infertility: A retrospective register study.	To further evaluate the risk of male infertility after inguinal hernia mesh repair.	Study group: All men from SHR born 1950-89 and operated between 1992 and 2007. Cross linking with the Swedish Patient Register for the diagnosis male infertility.	Inguinal hernia mesh repair is not associated with a clinically important risk of male infertility.

Introduction

In the beginning was inguinal hernia surgery. Is this a historical or religious remark? No it is certainly not. When I was a young surgical resident at the small hospital in the city of Hässleholm, primary inguinal hernia repair was the first operation I learned to perform. After doing two operations with a senior surgeon instructing me I started by myself. I did at least six inguinal hernia repairs each week for about three months. I still do not know if the method of repair I was taught had any name. Today it is often called "my way", but it was most likely a modified Bassini repair. It was made with interrupted resorbable sutures and with tension. The patients could not walk in an erect position the first days after the repair. I met them all four weeks after surgery but I do not know the long-term results.

Inguinal hernia surgery was not considered to be something special, just an operation for beginners – something that every surgeon had to do now and then. All surgeons at my age aimed for higher ground, which was gastrointestinal surgery. Of course recurrences occurred and these were repaired with an open preperitoneal sutured herniorrhaphy. The only femoral hernias I came across were those that were incarcerated. Probably I must have missed some.

In the early 90s I learned the Shouldice repair and for some years I felt as if I was updated. Then both the Lichtenstein hernioplasty and the laparoscopic repair methods became popular and some surgeons even started to call themselves hernia experts. For a long time it was very difficult for me to accept the fact that a mesh in the groin was the best solution for grownups with symptoms and findings of an inguinal hernia.

Classification and symptoms of hernia in the groin

The normal and pathological anatomy of the groin is very complex and has been studied for about 2000 years. In the 18th and 19th century the knowledge improved and most anatomical structures of the groin were described.
The difficulty in understanding the anatomy of the groin is due to at least four different factors:

- The three-dimensional relationship between the muscular, fascial and aponeurotic layers and the way they are changed due to the hernia disease.
- The role and the vulnerability of the structures that are passing through and beside the inguinal canal like the vessels, the nerves and the vas deference.
- The dynamic anatomical changes due to body position, abdominal pressure, diseases and previous operations.
- The need to recognize the anatomical structures, whether seen from the anterior or the posterior side of the abdominal wall.

A groin hernia is defined as a protrusion of abdominal cavity contents or preperitoneal fat through a defect in the groin area, irrespective of whether this is preformed (congenital) or acquired.

There are several classifications for groin hernias but the most commonly used is based on the anatomy of the hernia. Within this simple classification, there are three groups of hernias in the groin. A medial or direct hernia is one that protrudes medially to the epigastic artery and above the inguinal ligament. A lateral or indirect hernia protrudes laterally to the epigastric artery, above the inguinal ligament. A femoral hernia protrudes just below the inguinal ligament medial to the femoral vein. The term inguinal hernia refers to the lateral and medial ones but excludes the femoral ones.

Although the femoral hernia is regarded as a separate entity, in the clinical situation it is usually considered together with the medial and lateral inguinal hernias. This is not only because it is situated in almost the same anatomical region. It is mainly due to the fact that during clinical examination it is often difficult to differentiate between an inguinal hernia and a femoral hernia, especially in women. The two terms inguinal hernia and groin hernia are often wrongly used as synonyms. There is no singular Swedish term that corresponds to the English term groin hernia.

The groin hernias can also be divided into primary and recurrent hernias. Depending on the findings during the clinical examination hernias can be divided into reducible and non-reducible. In a non-reducible hernia the contents of the hernia sac cannot be reduced into the abdomen.

Non-reducible hernias can be chronic (accreta) or acute (incarcerated). The non-reducible acute hernia is called strangulated in two different situations, i.e. when the content of an incarcerated hernia is deprived of its vascular blood flow and becomes ischemic or when an incarcerated intestine becomes obstructed. Sometimes both situations occur at the same time.

Groin hernias can be asymptomatic. When symptoms occur, pain and discomfort are the most common. Large hernias can also give cosmetic problems due to their size. Most other symptoms are connected with complications of the hernia. A previously known hernia that becomes incarcerated often means increased local pain. If it is also strangulated it can give symptoms due to intestinal obstruction, ischemia of the hernia contents and organ perforation. The symptoms of a severe hernia complication include nausea, vomiting, abdominal pain, local groin swelling and

pain. Depending on the severity of the acute general symptoms the local groin symptoms are quite often unnoticed not only by the patient but also by the examinating doctor.

Frequency of groin hernias

The groin hernia disease has probably existed since the beginning of mankind. The shorter length of life probably lead to a lower prevalence of acquired hernia since few reached the age when hernias are common. However the congenital form of the inguinal hernias has most likely existed in almost the same frequency, since it develops during fetus.

The disease was already known and described in ancient times. Testimonies have been found as far back as in manuscripts from around 1550 BC. Signs of hernias have been found in mummies[1-3].

The incidence of groin hernia nowadays is not exactly known. However, in Sweden the incidence of groin hernia operations is approximately 200 per 100 000 inhabitants. Most of these operations are due to inguinal hernias. Thereby inguinal hernia repair is one of the most common operations performed by general surgeons. Inguinal hernia is most common in men. In the western world 27% of all men but only 3% of all women undergo an inguinal hernia repair during their lifetime[4].

As mentioned above femoral hernias are often clinically misdiagnosed as inguinal. Only 1% of the groin hernias in men are femoral hernias but 24% of the groin hernias in women are femoral[5].

Who needs inguinal hernia surgery?

Surgery is the only curing treatment for an inguinal hernia. Hernia symptoms in patients that can not be operated on, due to poor health or an unwillingness to be operated on, can sometimes be reduced by a hernia bandage (truss). Trusses are however not very comfortable and do not prevent strangulation.

All hernias do not need surgery. Asymptomatic inguinal hernias in men can most often be left without surgical intervention. Conservative management and delay of surgery until symptoms occur is termed watchful waiting[6,7]. The only important reason to operate an asymptomatic inguinal hernia is to reduce the risk of strangulation. In men this risk is low but since that risk is considerably higher in women, due to the higher frequency of and often misdiagnosed femoral hernias, it is often recommended that women with inguinal hernias are operated upon. On the other hand many patients who undergo an emergency operation due to a strangulated

hernia do not know that they have a hernia or in case they know, this has not bothered them at all.

Repair techniques

Bandages (truss) have been used for 3000 years. Inguinal hernia surgery can at least be traced back to Alexandria 300 BC. At that time the anatomical knowledge was limited and the surgical techniques seem to have included closing of the hernial sac with or without removing the ipsilateral testis.

150 years ago the surgical repairs were performed subcutaneously including ligation of the sac, narrowing of the external opening and reinforcement of the anterior wall. The recurrence rates were depressingly high, almost 100%. Many authorities stated that hernia surgery should not be performed.

Technical improvements like better sutures together with improved anatomical knowledge as well as new anaesthetic and antiseptic methods helped introducing "modern" repair techniques for inguinal hernia surgery. Between 1870 and 1900 a lot of new repair methods were introduced, often accompanied with very promising results.

On the following pages is a short description of some of the most popular repair methods /techniques used for the last 140 years. They are in some cases partly described according to modern adaption i.e. the original repair was not always exactly the same. Of course numerous other techniques have been described and used. The years of the publications of the different techniques have been found at PUBMED[8]. When the old original publications could not be identified through this database, the references have been found in the publications on hernia repair history[1-3,9-11]. The name of the surgeon who first described a new repair technique in a medical journal and the year of his first publication on this subject are not always easy to find. It also depends on if one accepts publications in more than the English language. I have made no difference in whatever language a repair technique was first described. Publications on anecdotal case reports have been omitted in favour of longer series of operations, preferably with results included.

The sutured repairs

The Marcy repair: Described[12] in its initial form by Henry O. Marcy[13] 1871 who also promoted the aseptic technique in surgery. It consists of high ligation of the hernial sac and narrowing of the internal ring. Nowadays the technique is sometimes used for lateral hernias in children and in growing youths. In 1892 Dr Marcy published a textbook of more than 400 pages on the subject of hernia[14].

The Bassini method: Initially reported in Italian[15] by Eduardo Bassini[10] 1887. Two years later he published a large monograph in Italian[16] on his technique, including many beautiful pictures, but the method was more widely recognized when his monograph was translated to German and republished[17] again 1890. Dissection of the inguinal canal, defining of the hernial sac, high ligation in case of a lateral sac and incision of the posterior floor were essential. The posterior floor was then reconstructed by interrupted nonresorbable suturing of the oblique internal muscle, the transverse abdominal muscle and the transverse fascia to the iliopubic tract and the inner parts of the inguinal ligament. This also led to a narrowing of the internal ring. Bassini included follow up results[10] for up to 4½ years with a recurrence rate of 3%.

The Halsted procedure: William S. Halsted[18] briefly first wrote about[19] his repair method 1889 and then made a more complete publication[20] on it in 1893. In many aspects it was performed like the Bassini method but the cord excised of its superfluous veins was transposed to a position above the external oblique aponeurosis. He later modified his method and omitted the transposition of the cord and instead covered it with both the internal and external oblique muscles[21]. Halsted's recurrence rate was 4% after at least four years of follow-up.

The McVay hernioplasty: It was first described by Georg Lotheissen[22] in 1898 but described again and popularized by Chester B. McVay[23] in 1941. The posterior wall was repaired by interrupted suturing. Medially the rectus sheet was adapted to Cooper's ligament and laterally the transversalis fascia was adapted to the femoral sheet. By this both the femoral and the internal ring were narrowed. McVay recommended the use of this method for medial, femoral, large lateral and recurrent hernias. He reported a recurrence rate of less than 1% after 1-11 years of follow-up[24].

The Shouldice repair: Often regarded as described in 1953 by Earle Shouldice in his only bibliographied publication[25]. In fact the description in that publication is not similar to the modern repair method wearing his name, described and published four years after his death[26]. This was basically a Bassini modification. The posterior repair was using the same layers but the adaption was made by a series of at least 3 nonabsorbable running sutures. The technique is regarded as the best of the sutured

repairs[27]. The Shouldice Hospital has reported of a recurrence rate of 0,6% after 17 years[28].

Nyhus original posterior preperitoneal operation: Lloyd M. Nyhus first described his preperitoneal repair method[29,30] in 1959. After opening the inguinal preperitoneal space the hernia was reduced and the transversalis fascia reapproximated to the iliopubic tract. The method was especially suitable for recurrent hernias and those involving incarcerated or strangulated bowel. Nyhus frankly reported that for primary hernias his results could not compete with the results from the Shouldice hospital[31]. Dr Nyhus edited and wrote the first editions of the famous modern textbook on hernia surgery that is still having his name in the title[32].

Open anterior mesh repairs

The Lichtenstein hernioplasty: In 1986 Irving Lichtenstein introduced the term tension-free hernioplasty[33] and in 1987 he published a personal series of more than 6000 repairs[34] reporting a recurrence rate of 0.7%. At that time he recommended invagination of an indirect hernia sac and suturing of the transversus abdominis aponeurosis to the inguinal ligament including narrowing of the internal opening medially to the cord and in case of a direct or recurrent hernia the posterior wall should also be reinforced by a mesh.

In 1989 Lichtenstein published his improved, and nowadays often called original method[35], where he no longer performed a sutured repair of the posterior wall, he just reinforced it by bridging the defect with a mesh that was sutured with a continuous monofilament nonabsorbable suture. The method was further improved in the early nineties[36] with recommendations of larger, slightly relaxed mesh, medial mesh overlap, crossing and suturing of the tails of the mesh lateral to the cord and only interrupted absorbable sutures on the upper edge of the mesh. The reported recurrence rate was further decreased.

As all popular methods it has been further modified not only by Lichtenstein's successor Amid[37] but also by many other surgeons. An EHS guideline published in 2009, states that it can be advisable to close a large direct hernia defect of the posterior wall, tension-free with continuous soluble sutures until a flat posterior wall has been created with a normal internal ring[38]. It is still debated whether surgeons should use the original method or the modified ones.

Plug and Patch or Rutkow-Robbins technique: The plug technique was developed and described by Alan Robbins and Ira Rutkow[39] in 1993. An umbrella shaped polypropylene plug was inserted into the hernia defect of the posterior wall acting as a sublay mesh and combined with an onlay flat mesh. They reported a recurrence rate of 1% for primary hernias on up to six years of follow up. It is well worth noting that Dr Rutkow has retired from clinical practice and now works as an

author of medical history. He has written at least six publications on hernia history[10,18,40-43].

Open posterior mesh repairs

The Stoppa method: This technique developed by many but popularized by René Stoppa[44,45] was performed by a low abdominal midline incision into the preperitoneal space. This gave the surgeon access to the entire bilateral myopectineal orifice of Fruchaud and a large mesh could be inserted completely overlapping all inguinal and femoral orifices.

Nyhus modified posterior preperitoneal operation: Later on in his life Nyhus modified his original method[29] by applying a mesh in the preperitoneal space after repairing the defect in the transversalis fascia[31]. He recommended this procedure especially for recurrent hernias.

Endoscopic posterior mesh repairs

IPOM (IntraPeritoneal Onlay Mesh): In 1992 Charles Filipi described a laparoscopic technique in which a mesh is placed intraabdominal, covering all inguinal and femoral orifices[46].

TAPP (TransAbdominal PrePeritoneal repair): Maurice Arregui[47] described the method in 1992. By a transabdominal laparoscopic technique a preperitoneal mesh is placed covering all inguinal and femoral orifices.

TEP (Totally ExtraPeritoneal repair): Described in French[48] by Jean-Louis Dulucq in 1992. By the extraperitoneal laparoscopic technique a preperitoneal mesh is applied covering all inguinal and femoral orifices.

The Swedish Hernia Register

The register[5] was started in 1992 by Erik Nilsson. Today this register includes nearly 100% of all inguinal hernia operations performed on grown-ups (>15 years of age) in Sweden. More than 200 000 operations have been included in the register so far. The register is subsidized by the National Board of Health and Welfare and the Swedish Association of Local Authorities and Regions. Member hospitals also pay a small sum

to the register for each recorded repair. There are no commercial sponsors of the register.

The register includes information on method of repair, mesh type (if mesh is used) anaesthesia, anatomical circumstances including testicular status and general information about the surgeon, patient and surgical procedure. The register also includes information on adverse events after the procedure. Operation due to recurrence or chronic pain is identified if the patient is reoperated.

The unique Swedish personal registration number system makes it possible to trace all patients at any given time through the National Population Register and on any occasion registered. This means any further repair on the same patient, performed in Sweden, can be traced. It also promotes the ability to cross-link the database with other databases as long as ethic and official permissions are given.

The aim of the register is to survey the development of hernia surgery in Sweden, to create a reliable base for local evaluation of treatment outcome, to enable epidemiological studies and to support prospective randomized controlled trials. A nationwide report and reports specific for each unit are published each year. So far at least 35 publications and six academical theses have been published on data derived from the register.

In 2010 approximately 16 000 hernia operations were performed on grown-ups, at Swedish hospitals and private clinics. Day time surgery was three times more common than over night surgery. Nine percent were operations due to recur-rences and eight percent of the operations were performed on women. Only five percent of the patients were operated on bilaterally. The median age was 63 years.

Mesh was used in 97% and Lichtenstein was the dominating repair method (70%).The laparoscopic methods, especially TEP, was used in 13% of the operations. Notably the old suture repair methods and resorbable sutures were still in use although sparsely. The registered complication rate was 9%.

The development of meshes

Synthetic sutures have been developed since the late 1930s. Nylon (polyamid) was the first such fabric. The polyester multifilament mesh Dacron (Mersilene) was the first popular synthetic mesh[2] and it is still available for clinical use[49].

Polyethylene was developed in the fifties. The synthetic suture had many improved properties e.g. it was strong, inert, nonwettable, temperature resistant and could be used as monofilament. When knitted as mesh it was strong and stretchable. In 1958 the use of polyethylene mesh (Marlex 50) in hernia surgery was first reported by Francis Usher[50]. He further supervised the development of the polyethylene mesh prosthesis and how to use it in different hernia repairs. In 1963 an improved version was introduced under the name of Marlex mesh (Bard). This was made of

polypropylene. It was more temperature resistant, could be cut without frying and was two-way stretchable. Other similar products are nowadays sold under different names (Prolene mesh, Surgipro etc.). The use of polypropylene meshes in all sorts of hernia repairs has increased enormously during the last 50 years. When incorporated in the tissue, polypropylene mesh induces an inflammatory reaction. The resulting fibrosis that develops around the mesh helps enhancing the strength of the repaired tissue[2,51]. Usher suggested the mesh could be used not only to strengthen or buttress a sutured repair but also to bridge the defect. By the latter the relaxing incision became unnecessary and the tension became eliminated.

The properties of the polypropylene mesh have continuously been improved. The manufacturers now provide such meshes with low weight, large pores, different coatings, more flexibility but still with a good memory, combinations with resorbable parts and preshaped forms including plugs. Large pores permit local tissue growth in the pores. This and the monofilament are believed to be the factors that have made it possible to keep it in place even in most cases of infection. The size of the meshes used have increased over time, due to the knowledge that larger meshes than those initially used probably result in a lower recurrence rate[38,52].

Nowadays, meshes are used for all sorts of hernia repairs. The different hernias and repair techniques require meshes with different properties. For example a large ventral hernia requires a mesh with more strength than a small inguinal hernia. The hernia specialists need a portfolio of meshes with different properties and sizes. Two surgeons at the same clinic often means two preferences. New mesh devices usually promise improved properties but to a higher cost. In Sweden we also face the problem that the increasing costs have made the government increasingly interested in buying large amount of cheap meshes with as few different properties as possible, with the aim to reduce the cost of buying and storing the prosthesis.

The definition of what is a lightweight mesh has been unclear[53]. This fact and the increased amount of different mesh devices have motivated a classification system. The benefit of such a system would be to improve the quality control i.e. are some devices related with more adverse events. That knowledge would help the surgeons to decide what mesh device is best for the patient. Uwe Klinge has recently suggested a new classification were the different mesh devices are grouped regarding to their biological and clinical response[54].

- Class I: Large pore meshes (often low weight)
- Class II: Small pore meshes
- Class III: Porous meshes with special features
- Class IV: Meshes with films (no porous or micro porous)
- Class V: Three-dimensional meshes (preshaped, preformed, plugs etc)
- Class VI: Biologicals

Recurrences after inguinal hernia surgery

Ever since Bassini started publishing his data 125 years ago the recurrence rate has been the most studied and discussed complication of inguinal hernia surgery. Until about 40 years ago the result most often was the same as the frequency of recurrences. Many but not all of the inventors of the different repair methods or at least their clinics have published their results regarding recurrences. They are all excellent but, however, sometimes difficult to repeat by others. They are also retrospective reports from surgeons or clinics with special and personal interest in inguinal hernia surgery. There have been assumptions that the individual experience of the surgeon is a stronger factor than the repair method itself[11]. The conclusions made from the results have been criticised mainly because the results are retrospective and not from prospective randomized trials. Other problems mentioned are author bias, selection, financial gain and incomplete or varying follow up[55].

All recurrences are not reoperated. Thereby the recurrence rate and the cumulative incidence of reoperations are not exactly the same. However, according to the SHR[5], the cumulative incidence of reoperations due to recurrences within five years was 3% for primary and 7% for recurrent groin hernias (Figure 1). In the SHR[5] the primary inguinal hernias operated with Lichtenstein had a significantly lower risk of reoperation compared to all other repair methods[5]. On the other hand, preperitoneal mesh methods of repair for recurrent groin hernias have the lowest risk of reoperation[56].

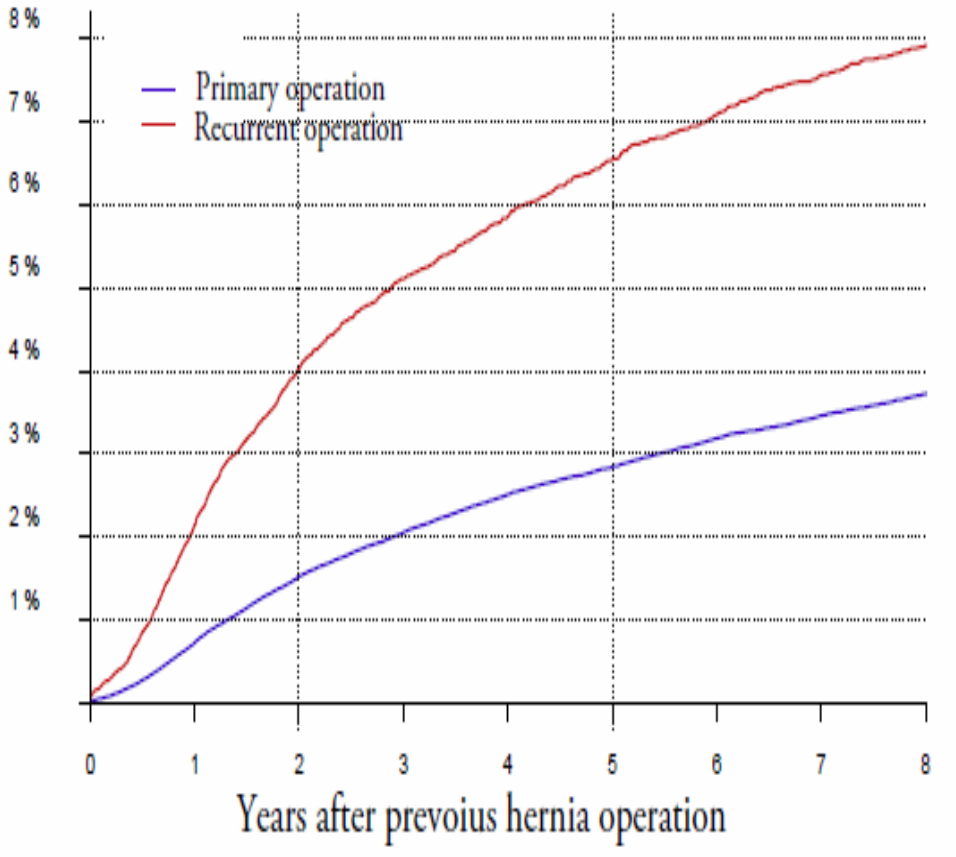

Figure 1 is illustrating the cumulative risk of being reoperated due to a groin hernia recurrence. The risk is doubled if the previous operation was due to a recurrent groin hernia. Reprinted with permission from the SHR Annual Report 2011.

Other complications after inguinal hernia surgery

During the last 20 years the recurrence rates have gradually decreased and inguinal hernia surgeons are nowadays also focused on other complications. The primary goal for most of the inguinal hernia surgeons of the last century was always the maintenance of the repair. Today's goal has been described as above, but it also includes the term "return to normal physiology"[53]. As always in surgery there are obvious technical complications during the operation like damage to the bowel, the structures of the spermatic cord and the vessels. The estimated incidence of injury to the vas deference is 0,3% in adult hernia repair[57]. The endoscopic repair methods have their own special complications including pneumatic problems and trocar site hernias.

Early postoperative complications include infection, severe pain, hematomas, seromas and urinary retention. Late complications include persistent pain, sensibility disorders and of course recurrences. Chronic pain has probably been the most studied complication for the last 10 years. The prevalence of chronic pain affecting normal activities or work is 0,5-6%[58]. Nerve damage is proposed to be the main reason for chronic pain[58].

Sexual problems secondary to an inguinal hernia are described. Sexual problems related to an inguinal hernia repair have been studied on males registered in the Danish Hernia Database. Among the identified problems were ejaculatory pain, genital pain, groin pain, pain related sexual impairment and erectile dysfunction[59,60].

Mortality is the most extreme complication. The risk in elective hernia surgery is almost zero. In emergency hernia surgery there is a substantial risk[61,62].

Mesh-related problems after inguinal hernia surgery

Most meta-analysis and guidelines that summarize RCT:s states that inguinal hernia surgery with mesh results in lower recurrence rates and less problems with chronic pain[38,63]. The latter is probably partly due to the possibility for the surgeon to perform a tension-free repair. The question if chronic pain after TEP is depending also on if fixation is performed and in what way, is not finally answered[52]. On the other hand there are specific problems and adverse effects due to the mesh itself.

Postoperative local infections at the site of the mesh are often more difficult to cure compared to sutured repairs. The mesh-induced foreign body reaction and the resulting fibrosis can give the patient a diversity of proven or suggested problems. These problems are partly related to the weight and the pore size of the mesh, to where the mesh is placed (anterior or posterior) and to the eventual fixation of the mesh. Among these problems are:

- Foreign body sensation
- Adherences to adjacent organs for example the bowel
- Perforation of adjacent organs
- Neuralgic pain due to induced fibrosis engaging the adjacent nerves

Strangulation or obstruction of structures passing through or adjacent to the mesh due to induced fibrosis and mesh shrinkage for example the structures of the spermatic cord.

Male subfertility and infertility

10-15% of all couples are infertile. This means they are not able to conceive a child even though the have had frequent, unprotected sexual intercourse for at least one year. Male infertility refers to the inability of a male to achieve a pregnancy in a fertile female. This is the case for at least 40-50% of all infertile couples.

The exact frequency of infertility in the whole male population is not known, since most studies are made on the male part in couples visiting a reproductive clinic because of infertility problems. It has been proposed that approximately 5% of all men are subfertile or infertile. Many of them have never consulted an andrologist due to the fact that they have difficulties in distinguishing between virility and fertility. They think a diagnose of infertility is a threat to their masculinity[64].

Male subfertility is most commonly caused by deficiencies in the semen. Idiopathic oligoasthenoteratozoospermia is the most common cause. This term refers to a semen analyze showing reduced sperm numbers, reduced sperm motility and increased abnormal forms of sperm[64].

Azoospermia means absence of sperm in the semen. It can be caused by hypothalamic-pituitary failure, testicular failure or obstruction. Men with obstructive azoospermia have normal spermatogenesis. The cause of obstruction can be congenital absence of vas deference, infectious epididymal obstruction, previous vasectomy and surgical damages to the vas deference[64].

Aims of the thesis

To compare two mesh-based inguinal hernia repair techniques namely Lichtenstein and TEP (Totally ExtraPeritoneal repair) in a prospective randomized controlled trial including one year of follow-up (short-term results). The primary outcome measures were sick-leave and postoperative pain. The secondary outcome measures were operation time, complications including recurrences, time to complete recovery and costs.

To compare the Lichtenstein and TEP repair techniques more than five years after the operation (long-term results). The primary outcome measures were patient satisfaction, impaired local sensibility, impact of the operation on day-to-day life and chronic pain.

To determine whether the use of mesh for bilateral male inguinal hernia repair in men of fertile age can cause male infertility i.e. increases the prevalence of male infertility, measured as involuntary childlessness.

To further evaluate the risk of male infertility after inguinal hernia mesh repair, in a large population-based cohort, by retrospectively cross-linking data from the Swedish Hernia Register and the Swedish National Patient Register.

Background to the studies

Background to study 1

At the Department of Surgery at Lund University Hospital, as well as in many other clinics the Lichtenstein[35] and the laparoscopic inguinal hernia repair techniques were introduced almost simultaneously in the mid 90s. This was just a few years after the Shouldice technique[26] had been popularized in Sweden. Other methods, seldom used today, were still dominating (Figure 2). The technical enthusiasm surrounding the new laparoscopic techniques increased the surgeons' interest in many adaptable fields including hernia surgery. Promises of fewer recurrences, less postoperative pain and shorter sick leave also gained our attention[47,65-69]. Nationally there was a demand for better results in hernia surgery[70] and the Swedish Hernia Register was initiated[71]. Our modern cost-effective daytime surgery ward with high capacity[72] was a perfect unit for studies on this subject.

Despite the enthusiasm for everything that could be done with a laparoscope, the hernia specialists were not sure which was the best laparoscopic method, TAPP (transabdominal preperitoneal repair) or TEP (totally extraperitoneal repair). Just a few publications on studies comparing different laparoscopic and open methods were available[73-77]. The methods used in these publications were TEP[74,75], TAPP[73-77], IPOM[74,75] (IntraPeritoneal Onlay Mesh), plug and patch[74,75], simple closure of the defect[74,75] or a mixture of those mentioned[74,75]. One prospective randomized trial comparing TAPP and Lichtenstein[73], one comparing TAPP and a mixture of different open repair methods[76] and finally one comparing TAPP and a sutured repair described by Moloney[77,78] were available. To our knowledge there was no large published prospective randomized trial comparing TEP and Lichtenstein at that time and the need for such a study had been discussed[68].

We therefore decided to perform a prospective randomized trial comparing the Lichtenstein repair technique with TEP. One of the reasons for choosing TEP as the laparoscopic method was the possibility of performing hernia operations without entering the abdominal cavity and thereby minimize the risk of intraabdominal complications. The primary aims of the study were to compare sick leave and postoperative pain (estimated as total consumption of analgesics). Secondary aims were to compare operation time, complications including recurrences, time to

complete recovery after surgery and costs. In designing the study we aimed for one year of follow up including both questionnaire and clinical examination by an independent observer. We wanted the male patients included in the study to represent the normal mixture of male patients referred to a normal surgical clinic, which meant also bilateral and recurrent hernias.

Background to study 2

By the time study 1 was finished and published there were almost no published long-term results (> 5 years after surgery) of prospective randomized trials on this subject. One long-term study on TEP versus Lichtenstein based on questionnaires could be identified[79] and another long-term study comparing TEP with different open methods was found[80]. During the previous years the question of chronic pain after hernia surgery had also come into focus[63,81-83]. This was probably because the former main problem after hernia surgery, i.e. the recurrences, had become a less important problem since the widespread use of mesh, whatever mesh repair method preferred[63,82,84,85].

This motivated us to perform a long-term follow up including not just a questionnaire but a new clinical examination. When performing the follow up in study 1, we found that the findings at the clinical examination were not always in line with the patients' answers in the questionnaire. We decided to compare the results in both groups regarding impaired sensibility, patient satisfaction, impact of the operation on day-to-day life and chronic pain. The presence of recurrences was planned to be assessed again, being the best parameter to describe the quality of the surgery performed at the primary operation.

Background to study 3 and 4

The use of mesh had over time continued to increase both in Sweden and worldwide and the use of sutured repairs had steadily decreased (Figure 2). It was no longer an infected debate whether Lichtenstein or TEP was the method of choice. It had become more and more obvious that both methods had their advantages, although the Lichtenstein procedure was still the most commonly used (Figure 2). The Lichtenstein technique had the advantage of being easy to learn and reproduce even for surgeons outside clinics specialised in hernia surgery. Both methods could be used in clinical routine side by side at least in centers specialised in hernia surgery. Their different advantages for the patients motivated their continuing coexistence.

The problems of recurrences and chronic pain were now meticulously studied and discussed even if not completely solved. Other inguinal hernia surgery problems regarding mesh had gradually gained attention.

It was well known that an alloplastic mesh causes an inflammatory response and foreign-body reaction in the surrounding tissues. The resulting fibrosis of the inguinal wall was regarded as one of the reasons for the low recurrence rate. Whether or not the mesh was applied from an anterior approach, e.g. according to the Lichtenstein technique[35], or from a posterior approach, as in laparoscopic repair, it was placed in direct contact to the spermatic cord.

Several animal studies in various species (pig, rat, dog and rabbit) had reported that the structures of the spermatic cord also reacted to the mesh[86-90], especially the edge of the mesh[86]. Thickening of the wall of the vas deferens with narrowing and obstruction of the lumen at the site of the mesh but not proximal to it had been observed and discussed[86]. Others had found proximal dilatation but no thickening of the wall of the vas deferens[87]. Decreased arterial perfusion in the testis[88,91] and spermatic venous thrombosis[89] had also been reported. On the other hand one animal study showed no mesh effect on testicular hormonal function and no induced testicular cell apoptosis[92] and yet another animal study showed no mesh effect on the spermatic cord, the testis or the sperm when the mesh was placed on the peritoneum (IPOM)[93]. One study had shown beneficial effects on the integrity of the vas deferens when using lightweight mesh[86] whereas another study did not find any difference in inflammation and fibrosis comparing heavyweight with lightweight mesh[94].

A few human reports had suggested that the use of mesh for male inguinal hernia repair could cause male infertility, most often by obstructive azoospermia[95,96]. Men operated with bilateral mesh hernia repair or men with unilateral repair and impairment of the contra lateral testis had been considered to run a greater risk. Some authors had even suggested that the risk of infertility after mesh repair was of such importance that surgeons should avoid mesh techniques for young men. Since most of these reports were based on a limited number of human cases[95,96] or animal studies, their conclusions had been questioned, and some even considered the studies inadequate and not valid enough for more explicit conclusions[97].

There had also been discussions about whether or not the proposed risk of infertility was of such importance that some or all patients undergoing hernia surgery should be informed in detail preoperatively, even if this could cause some patients to choose a method associated with an increased risk of recurrence and/or chronic pain[95,97]. Most authors agreed that we still did not know whether the proposed risk for postoperative infertility was relevant and more human studies were demanded[86,97,98].

In conclusion there was a need for human studies addressing the question of whether the use of mesh for male inguinal hernia repair was associated with an increased risk of postoperative infertility. To use the Swedish Hernia Register seemed a possible way to explore the question further on.

The aim of study 3 was to determine the prevalence of infertility, measured as involuntary childlessness, in men who hypothetically ran a higher risk of obstructive azoospermia, i.e. those in fertile age who had undergone bilateral mesh hernia repair.

The aim of study 4 was to further evaluate the risk of male infertility after inguinal hernia mesh repair, in a large population-based cohort, by retrospectively cross-linking data from the Swedish Hernia Register and the Swedish National Patient Register.

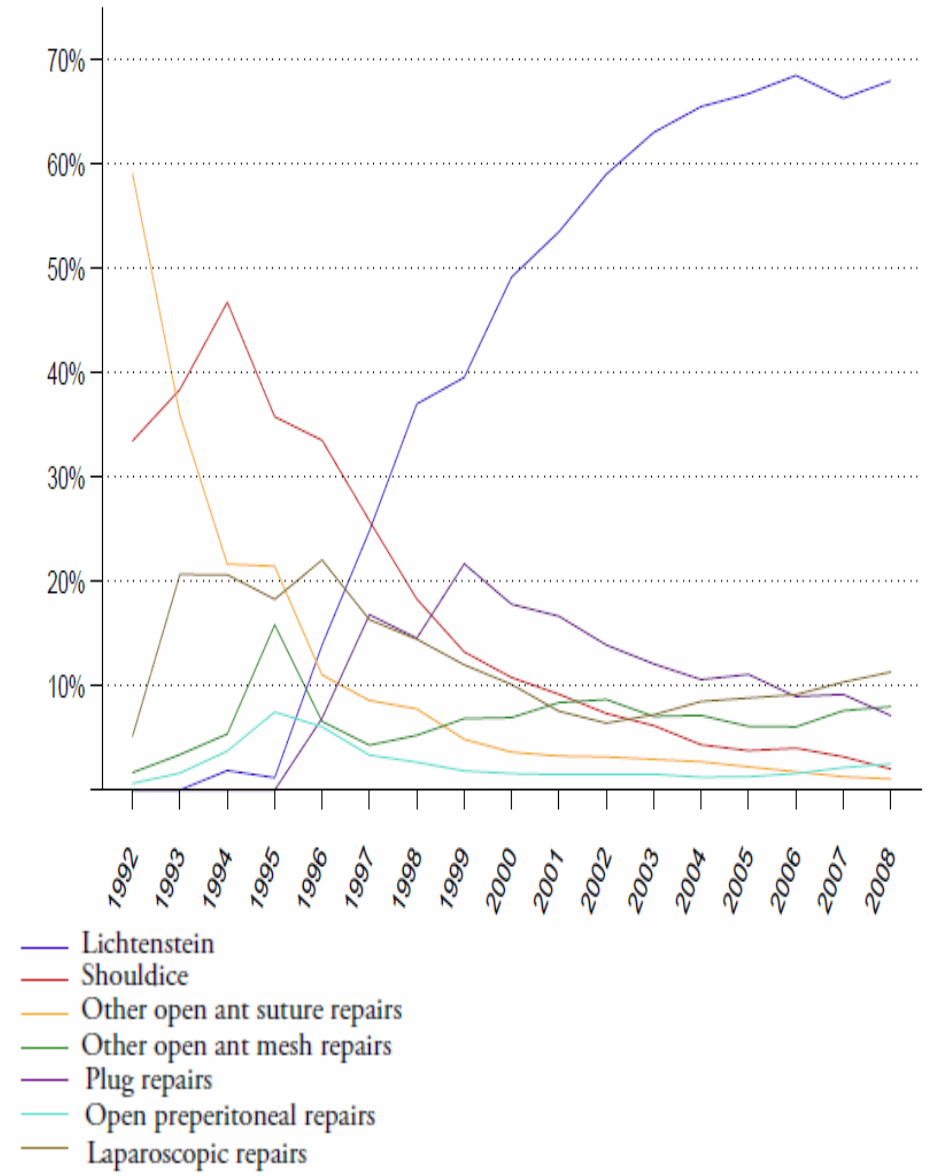

Figure 2. Operating techniques used for inguinal hernias 1992-2008. This figure is based on 174 538 hernia operations in Sweden that were registered in the Swedish Hernia Register (SHR). It illustrates that the mesh methods almost replaced the sutured techniques during this time period. Reprinted with permission from the SHR Annual Report 2008.

Subjects and designs

Patients and design of study 1

Between 1996 and 1997, 185 men, aged 30 to 65 years, referred to the Department of surgery, Lund University Hospital, Lund, Sweden, for primary or recurrent inguinal hernia repair were enrolled in the study. A flow chart summarizing the study is shown in figure 2.

The patients were randomised to either TEP or Lichtenstein. After randomisation, but before surgery, 17 patients were excluded from the study and the 168 remaining patients were included in the study.

Surgery was performed by 3 of the authors, mainly as day-care surgical procedures. The TEP operation was performed under general anesthesia. A 10x15 cm polypropylene mesh (Marlex) was used and it was fixed to the abdominal wall and the ligament of Cooper with a screwstapler. In the Lichtenstein group an identical mesh was used. The Lichtenstein repair was performed under regional or general anesthesia, depending on anesthesiologic considerations or patient preference.

Paracetamol and dextropropoxyphene were used as postoperative analgesics. Furthermore, the patients were asked to complete a comprehensive questionnaire once daily during the first week and then weekly the following 5 weeks. The questionnaire included questions on complications, such as fever, local swelling, redness, and tenderness. Questions were also asked about how much the operation influenced the ability to carry out daily activities and the ability to move, end of sick leave, and time to complete recovery (i.e. when the patients believed that they were quite recovered from the operation). Pain was estimated on a visual analogue scale, from painless to unbearable pain. They received thorough information regarding the specific items of the questionnaire by a research nurse. In addition, the patients were given instructions regarding self-medication with analgesics, which was allowed to a maximum of 4 g of paracetamol and 400 mg of dextropropoxyphene per 24 hours. They were also informed that they could rely on the strength of the repair, and they were encouraged to return to unrestricted activity and work as soon as possible. A certificate of illness, which entitled the patients to receive sick pay for a maximum of 7 days was prescribed by the responsible surgeon and extended at the request of the patient for not more than 7 days at a time.

Follow-ups were done 1 and 6 weeks after surgery by the research nurse. The wounds were inspected, analgesic consumption was reported by the patient and complications were noted. At a clinical one year follow-up the patients were examined by an independent surgeon (MH) and postoperative symptoms were registered.

Calculations of costs were made for direct costs (equipment, operation time, and hospital stay) and indirect costs (sick leave) to estimate the health cost.

Statistical methods used in study 1

In a pilot study, we found that TEP patients differed in analgesic consumption and number of days on sick leave compared with Lichtenstein patients. Thus, with an α error of 0.05 (2-sided) and a power of 0.90, it was found that 70 patients in each arm would be sufficient to detect a difference in 12 days of sick leave in the open group and 8 days of sick leave in the TEP group. The previous calculated sample size would also, with an α error of 0.05 and a power of 0.92, detect a difference in paracetamol consumption of 10.5 g in the open group and 6.5 g in the TEP group.

Analyses of outcome measures were performed on an intention-to-treat basis. The results for continuous variables are presented as mean ± standard deviation, if not stated otherwise. For categorical data, absolute numbers in addition to percentages are given. For numeric data, differences between groups were analyzed with the unpaired *t* test, except for data with skewed distribution of numbers, when the Mann-Whitney *U* test was used. The $\chi 2$ test was used for categorical data, except when expected frequencies were less than 5, when the Fisher exact test was used. A probability level of a random difference of *P* less than 0.05 was considered significant.

Patients and design of study 2

Study 2 was a long-term follow up of the patients included in study 1. It was planned after study 1 was finished. A flowchart summarizing both studies is shown in figure 3.

All participants were mailed a reply-paid comprehensive questionnaire at a minimum of 6 years after the operation. This included questions regarding pain in the groin or testicle, impaired local sensibility, complete recovery, impact of the operation on day-to-day life, and whether the patient was satisfied with the results of the operation and recovery as well as questions about the presence of a recurrent lump in the treated groin, operation for recurrent hernia, and development of a lump in the contralateral groin.

All patients who returned the questionnaire were contacted subsequently by telephone for complementary questions and information. They were also offered a

free of cost follow-up consultation at the outpatient clinic by the same independent surgeon (MH) who performed the 1-year follow-up in study 1. At this follow-up, the inguinal area was examined, impaired sensibility was recorded, and atrophy of the testicle was registered. The presence of a recurrent hernia, which was based on clinical examination that showed a palpable reducible lump in the treated groin or in clinically uncertain cases with herniography, was recorded. When applicable, the patient was asked to provide a more thorough pain history.

Statistical methods used in study 2

Analyses of outcome measures were performed on an intention-to-treat basis. The results of continuous variables are presented as median (range) if not stated otherwise. For categorical data, absolute numbers in addition to percentages are provided.

For numeric data, differences between groups were analysed with the Mann-Whitney U test. The $\chi 2$ test was used for categorical data, except when expected frequencies were less than 5, when the Fisher exact test was used. A probability level of a random difference of P less than 0.05 was considered significant.

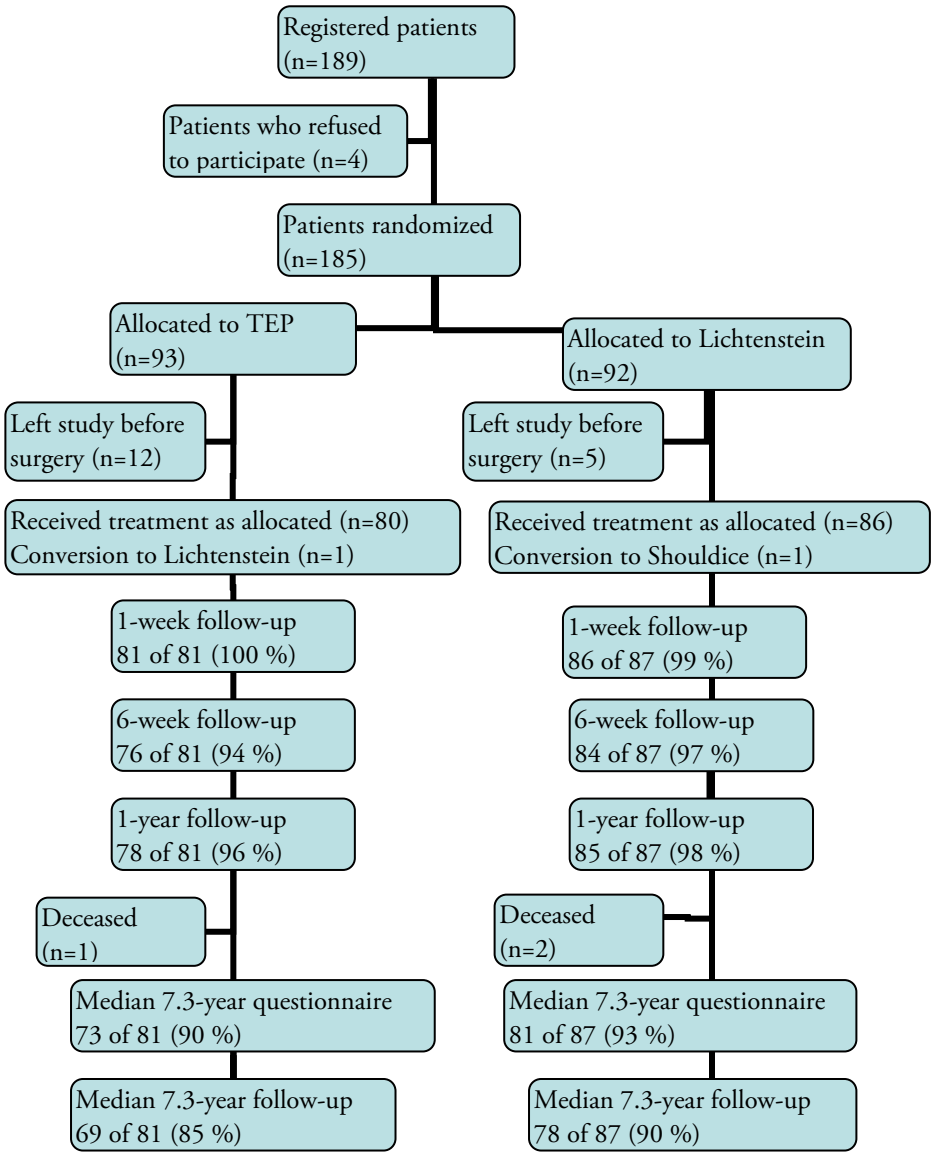

Figure 3. Flow chart illustrating study 1 and 2. This figure is reprinted with permission from publication 2 but slightly expanded and changed in layout to make it better describe both study 1 and 2. © 2008 Mosby, Inc.

Patients, controls and design of study 3

Study 3 was a prospective designed study based on data from the Swedish Hernia Register (SHR)[5]. A flowchart summarizing this study is shown in figure 4.

Two groups were assembled from the SHR, one consisting of men operated bilaterally with mesh and one group consisting of men operated bilaterally without mesh. The groups were matched for age and time elapsed since last repair. Since bilateral repairs without mesh were much less frequent than repairs with mesh, thereby limiting the size of the study, this group was identified first. The mesh group was then matched to the non-mesh group two cases to one. The included men were aged 18-55 years. Those who had undergone more than one repair in the same groin were excluded. A second control group, matched for gender, age and marital status, was assembled from the National Population Register. This control group consisted of one subject for each patient operated bilaterally with mesh.

In April 2009, all patients and controls received the same questionnaire, including questions on involuntary childlessness, infertility investigations and number of children (Table VI-VIII). There was also an additional question inquiring about previous hernia repair addressed to the controls assembled from the general population. Three weeks after the questionnaire was distributed a reminder was sent to the non-responders.

Statistical methods used in study 3

The difference in numbers of children born after the last repair was analysed with the t-test. For all other questions the differences between the groups were analysed with the $\chi 2$ test. A probability level of a random difference of P less than 0.05 was considered significant.

The results for continuous variables are presented as mean $\pm$ standard deviation (SD) if not stated otherwise. For categorical data, absolute numbers in addition to percentages are provided. All three groups were included in comparisons regarding the first two questions (involuntary childlessness and investigations for infertility the last five years). The remaining questions were not applicable for the control group from the general population.

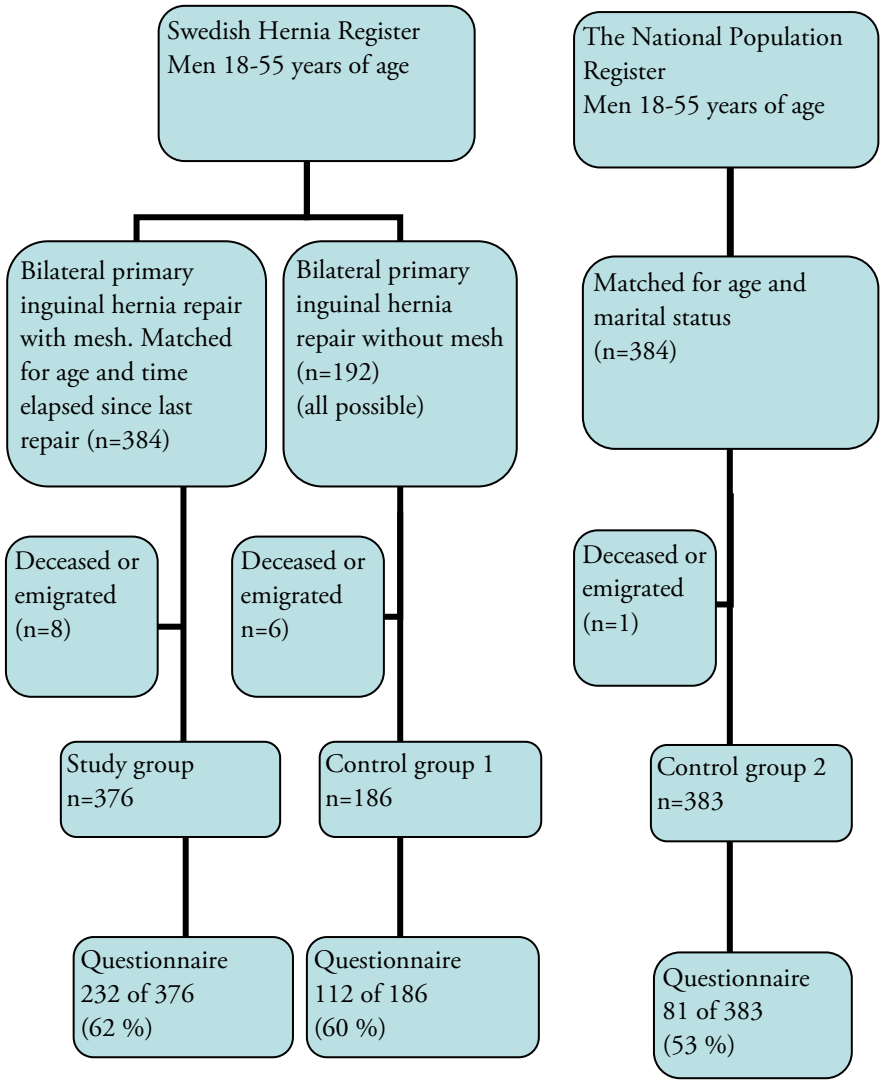

Figure 4. Flow chart illustrating study 3.

Patients, controls and design of study 4

Study 4 was a retrospective register study with two separate analyses. A flowchart that summarizes this study is shown in figure 5.

All men born between 1950 and 1989 who were registered with a hernia repair in the Swedish Hernia Register (SHR) between 1992 and 2007 were included. Men with both hernia repair and the diagnosis infertility were identified by cross-linking the SHR with the Swedish National Patient Register by searching for the diagnosis "male infertility" (ICD code N46.9). It was not possible to obtain the ICD subcodes (fifth position) for the aetiology of infertility from the Swedish National Patient Register.

Analyse A: Cumulative incidence of infertility in men operated for groin hernia versus the general population

The observed cumulative incidence of infertility, estimated from the year after the first hernia repair, was compared with the expected cumulative incidence, i.e. the calculated incidence that would be expected if it was identical to the general age-matched Swedish male population. The expected cumulative incidence was estimated by adding the incidences of newly diagnosed infertility in the total Swedish male population each year after the hernia repair.

The incidence of infertility each year was determined by the ratio between the number of men with the diagnosis of infertility and the total number of men born within the same five-year stratum in Sweden. The total relevant population in Sweden was obtained from Statistics Sweden. For men who had undergone more than one repair, the incidence was determined from the year after the first repair.

In the analyses, the men with at least one hernia repair were divided into five groups depending on the repair:

I. Unilateral repair without mesh
II. Unilateral repair with mesh
III. Bilateral repair without mesh
IV. Bilateral repair with mesh on one side
V. Bilateral repair with mesh on both sides

Men who had undergone more than one repair on either side were included in a separate group since they constitute a more heterogenic group and surgical trauma to the vas deferens may have been more extensive. No distinction was made between bilateral repair in one synchronous procedure and bilateral repairs on two separate occasions.

Analyse B: Mesh versus non-mesh repair and risk of infertility

The observed cumulative incidences of infertility in group I and II (unilateral repair with or without mesh) were compared. The observed cumulative incidences of infertility in group III, IV and V (bilateral repair without mesh or with mesh on one or both sides) were compared.

Statistical methods used in study 4

Analyse A: Cumulative incidence of infertility in men operated for groin hernia versus the general population. The differences between observed and expected cumulative incidence in each group were tested with the $\chi 2$ test.

Analyse B: Mesh versus non-mesh repair and risk of infertility Two separate multivariate logistic analyses with infertility as the dependent variable were performed, one for men who had undergone bilateral repair and one for those who had undergone unilateral repair. In both analyses adjustments were made for age (patients born 1965 or later versus patients born before 1965) and years elapsed since the first repair. In the analysis of those who had been bilaterally repaired, the laterality was treated as a three-stage ordinal scale (no mesh, mesh on one side and mesh on both sides).

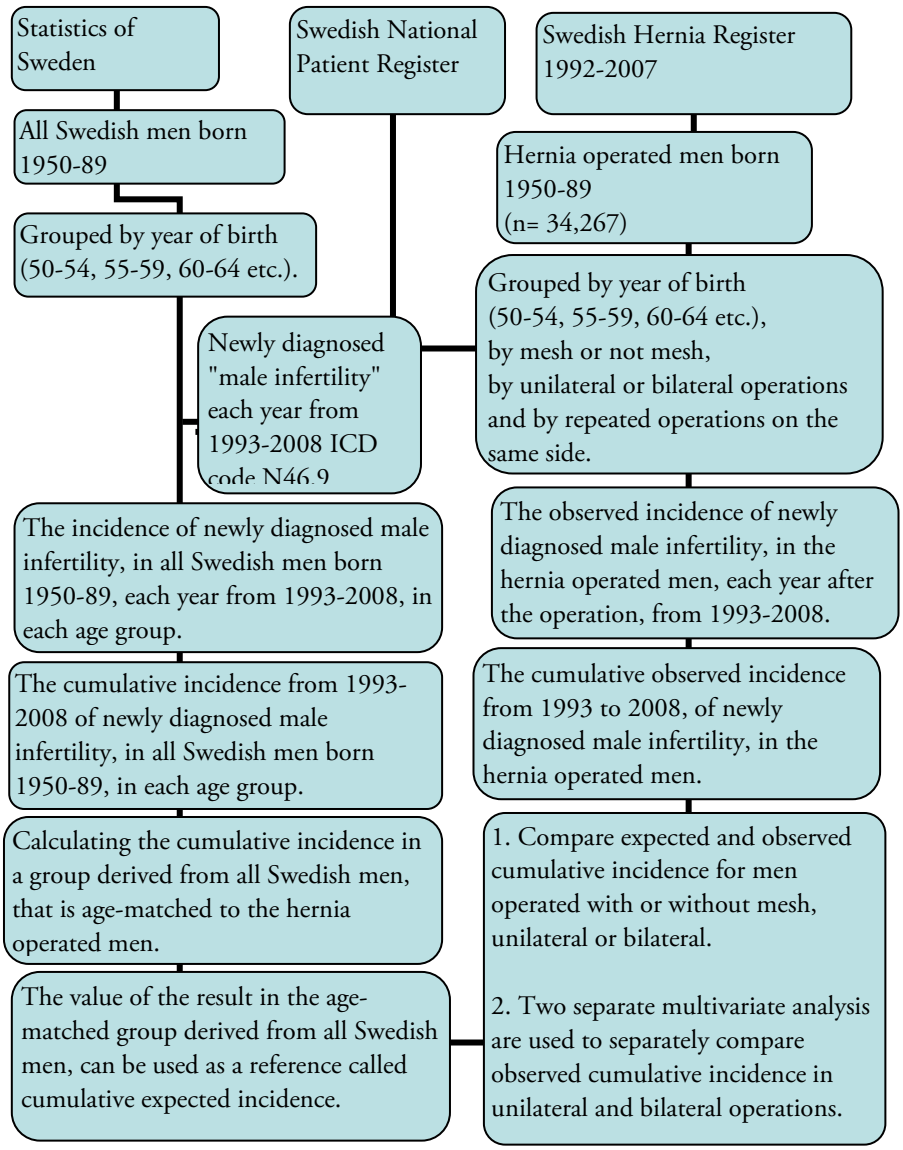

Figure 5. Flow chart illustrating study 4

Ethics

The Ethical Committee of the Medical Faculty of Lund University approved study 1 and 2. Umeå Ethics Review Board of Umeå University approved study 3 and 4. In study 1 and 2 the risks for the participating patients were considered low. In study 3 and 4 there were no physical risks for the participants. The potential benefits from all the studies were improved surgical treatment and exploration of a proposed risk of infertility after inguinal hernia mesh repair.

Results

Study 1 (TEP versus Lichtenstein, short-term results)

Of the 168 patients included in the study, 140 had primary hernia (including 10 bilateral cases) and 28 patients had recurrent hernia. Twenty patients had previously undergone hernia surgery contralaterally. 81 patients were randomized to the laparoscopic group, and 87 to the open group (figure 2). No significant difference was seen in age, preoperative symptom and signs, and type of daily occupation between the two groups of patients.

Perioperative complications are listed in Table I. Seven patients (9%) in the TEP group and four (5%) in the Lichtenstein group had perioperative complications (P =0 .36). None of the four patients with epigastric artery bleeding needed blood transfusion. However, for one of them, a patient in the TEP group, the operation had to be converted to an open tension-free repair because of the bleeding. The three electrocardiographic or heart rhythm changes were all of temporary nature. In both cases of registered injury to the peritoneum, we were able to maintain the pressure of the pneumopreperitoneum and no conversion had to be undertaken. One patient had acute airway obstruction for unknown reason during an operation with general anesthesia. In the open group, one patient happened to have a small serosal tear in the colon of a sliding hernia. This motivated the surgeon to change to a hernia repair according to Shouldice (to avoid mesh). Except for the two patients with an injury to the peritoneum, all the patients with perioperative complications stayed overnight for observation at the hospital.

A difference was seen in operating time in favour of the Lichtenstein technique. The operation time was 81 ± 27 minutes for the TEP group and 59 ± 20 minutes the Lichtenstein group ($P < 0.001$).

The average hospital stay after surgery was 13.6 ± 6.9 hours in the TEP group and 12.4 ± 6.3 hours in the open group ($P = 0.24$). Sixty-three percent of the patients were discharged within 12 hours. Thirty-seven patients, 19 patients in the laparoscopic group and 18 in Lichtenstein group ($P = 0.95$), stayed overnight at the hospital for various reasons: perioperative epigastric artery bleeding (n = 4), perioperative electrocardiographic or heart rhythm change (n = 3), acute airway obstruction (n = 1), small preoperative serosal tear in the colon (n = 1), and

postoperative discomfort consisting of different combinations of nausea, dizziness, fatigue and pain (n = 29). The average hospital stay for these patients was 24 ± 4 hours. All patients were discharged within 30 hours. No difference was seen in hospital stay between patients who underwent operation according to Lichtenstein with regional or general anesthesia. Furthermore, no difference was seen in hospital stay between patients who underwent TEP or open surgery with general anesthesia.

The follow-up rates were 99% after one week, 95% after six weeks, and 97% after one year. At the follow-up one week after surgery, patients in the TEP group had consumed less analgesic than patients in the Lichtenstein repair group. In the laparoscopic group, patients had used a median of 5g (range, 0 to 28 g) acetaminophen versus a median of 11 g (range, 0 to 28 g) acetaminophen in the open repair group ($P < 0.0001$). For dextropropoxyphene, the corresponding figures were 400 mg (range, 0 to 2400 mg) in the TEP group versus 900 mg (range, 0 to 2800 mg) in the open group ($P < 0.0001$).

The patients in the TEP group returned to work earlier than the patients in the open group. This difference was more obvious in the subgroup of patients with labor work than among office workers (Table II). Patients in the laparoscopic group reported a shorter time to complete recovery than patients in the Lichtenstein group (Table II).

All the postoperative complications are shown in Table I. One TEP patient was reoperated after three days for small bowel obstruction. The small bowel was found to have herniated through a tear in the peritoneum that was created, but unnoticed, during the hernia repair. The laparoscopic reoperation was uneventful. Testicular pain was more common in the TEP group, occurred in the early postoperative period, and settled after a period of weeks or months. One year after surgery, all patients had normal testes on clinical examination. Hematomas were more often found in the Lichtenstein group. The Lichtenstein group showed a higher frequency of impaired sensibility in the inguinal area compared with the TEP group.

No recurrences were seen at the 6-week follow-up. However, two recurrences were found on clinical examination one year after surgery. Both were primary hernias operated with the TEP technique. In one of the two patients, the dissection at the TEP operation was reported as troublesome. The two recurrences have undergone reoperation with open repair.

One year after surgery, patient satisfaction with the hernia operation was estimated on a visual analogue scale, from 0 (the worst) to 100 (the best). The median value for the TEP group was 100 (range, 18 to 100) and for the open group was 98 (range, 30 to 100), $P = 0.53$.

The estimated costs in the laparoscopic group included costs of rerepair of the two recurrences and the small bowel obstruction. The direct costs of the TEP operation were higher than those of the group with Lichtenstein repair ($P < 0.001$). With inclusion of the indirect costs (i.e. cost for sick leave), the TEP technique was not more expensive than the open mesh repair ($P = 0.21$).

Table I. Complications and recurrences (yes/no)

	Lichtenstein, n=87	**TEP, n=81**	**P value**
Perioperative complications			
Epigastric artery bleeding	2/85	2/79	0.99
ECG or heart rhythm change	1/86	2/79	0.61
Injury to peritoneum	-	2/79	-
Acute airways obstruction	0/87	1/80	0.48
Serosal tear in the colon	1/86	0/81	0.99
Postoperative complications			
Bowel obstruction	0/86	1/80	0.99
Urinary retention	2/84	4/77	0.43
Constipation	6/80	8/73	0.50
Hematoma	18/68	7/74	0.03
Wound infection	2/84	0/81	0.50
Seroma	2/84	0/81	0.50
Hydrocele	0/85	1/80	0.99
Neuralgia	4/81	5/76	0.74
Testicular pain	6/79	19/62	0.003
Pain	22/63	14/64	0.22
Impaired inguinal sensibility	38/47	8/71	<0.0001
Recurrence (one-year follow-up)	0/85	2/76	0.23

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Table II. Number of days on sick leave and time to complete recovery

	Days on sick leave*			Days to complete recovery*		
Daily occupation	**Lichten-stein**	**TEP**	**P value**	**Lichen-stein**	**TEP**	**P value**
Manual labour	16±10	11±4	0.003	30±12	17±10	0.001
Mixed	10±5	8±5	0.08	13±10	13±11	0.98
Office	7±6	5±4	0.12	15±10	10±8	0.04
Retired	-	-	-	20±16	20±14	0.98
All	11±8	8±5	0.003	19±13	13±10	0.007

* Mean value ± SD

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Study 2 (TEP versus Lichtenstein long-term results)

Of 168 patients included in the prospective, randomized controlled trial herein called study 1, 165 patients (98%) were alive after a minimum of six years after operation. 154 of 165 patients (92%) answered the questionnaire and 147 patients (88%) were followed up at the outpatient clinic (figure 2). Median follow-up was 7.3 years (range, 6.1–8.9 years).

Overall, 89% of patients in the TEP group and 95% of patients in the open group reported complete long-term recovery (P = 0.23). In the questionnaire, patients were asked to estimate the impact of the operation on their day-to-day life on a visual analog scale, from 0 (no impact) to 100 (total impact). The median value for the TEP group was 4 (range, 0 to 86), and the median for he open group was 5 (range, 0 to 69) (P = 0.15).

Long-term complications are listed in table III on the next page. Permanent impaired inguinal sensibility was more common in the open group, whereas the proportion of patients with reported testicular pain was higher in the TEP group. Severe pain was only observed in six patients (four patients in the TEP group and two patients in the open group). However, only one patient reported a regular need of analgesic and long-term sick leave. Four patients in the TEP group and five patients in the open group reported that the operation had a long-lasting negative impact on their ability to move (P = 0.99). As reported in the first study, two recurrences were found one year after operation, both in the TEP group. At the long-term follow-up, one additional recurrence in the TEP group and 4 recurrences in the open group were

noted. In six of the seven recurrences, the diagnoses were based on clinical examination revealing a palpable lump in the operated groin. In the remaining patient, the clinical examination was uncertain, and a herniography confirmed the recurrence. In the questionnaire, the reported number of recurrences was eight. However, in one patient, clinical examination and herniography ruled out a recurrent hernia.

At the long-term follow-up three more patients, who were all in the TEP group, had undergone operations for conditions related to the hernia repair. One patient suffered from severe chronic testicular pain caused by impaired testicular circulation and an orchidectomy was performed. Still another patient developed an umbilical hernia that was repaired. Finally, one patient with severe inguinal neuralgia underwent a surgical exploration with neurolysis after long-term conservative treatment.

Table III. Long-term complications (yes/no)

	Lichtenstein, n=81	**TEP, n=73**	**P value**
Impaired inguinal sensibility	26/81	9/73	0.004
Groin pain	11/81	6/73	0.32
Testicular pain	1/81	10/73	0.003
Testicular atrophy	3/75	2/69	0.99
Umbilical hernia	0/78	1/69	0.99
Neuralgia	0/78	1/69	0.99
Hydrocele	0/78	1/69	0.99
Recurrence	4/78	3*/69	0.37
Contralateral hernia	13/81	15/73	0.47

*2 of 3 recurrences were diagnosed at the 1-year follow-up.

Study 3 (mesh/infertility: the prospective study)

Altogether 192 male patients aged 18-55 years, operated bilaterally without mesh, were identified in the SHR. They were matched 1:2 with 384 patients who were operated bilaterally with mesh and 1:2 with 384 men from the general population. There were eight patients in the bilateral mesh repair group, six patients in the non-mesh bilateral repair group, and one man in the general population group who had emigrated or deceased by the time the questionnaire was administrated.

The response rates were 232/376 (62%) in the bilateral mesh repair group, 112/186 (60%) in the bilateral non-mesh repair group and 181/383 (53%) in the control group. All data presented are based on the responders. Responders and non-responders did not differ in age and marital status (Table IV).

Table IV. Marital status

	Operated bilaterally with mesh n (%)	**Operated bilaterally without mesh n (%)**	**Controls from the general population n (%)**
Married	107 (46.1%)	50 (44.6%)	95 (47.0%)
Unmarried	95 (40.9%)	47 (42.0%)	93 (46.0%)
Divorced	30 (12.9%)	15 (13.4%)	14 (6.0%)
Total	232 (100%)	112 (100%)	202 (100%)

Mean age in the bilateral mesh repair group was 42.3 years ±8.8 years, 43.4 years ±8.8 years in the bilateral suture repair group and 43.1 years ±8.1 years in the control group. Altogether 179 (33%) were 40 years or younger when they answered the questionnaire.

There was no significant difference in age between the two hernia repair groups and the control group from the general population. Mean time elapsed since the last repair in the two groups from the SHR was 6.9 years ±3.3 years. There was no significant difference in time elapsed since the last repair between the two groups. Testicular atrophy or absence of the testicle on the side operated was noted in 6 (1.1%) of the repairs. Light-weight meshes were used in 17 patients (4.9%) of the mesh repairs. The mesh repairs were performed via an anterior approach in 435 (80%) patients and via a posterior approach, open, or laparoscopic, in 111 (20%) patients. There were 16 (8%) subjects in the control group assembled from the general population who stated that they had undergone hernia repair.

There were no significant differences between the groups for any of the questions, including questions inquiring about involuntary childlessness, infertility

investigation, and number of children (Table V-VI). Subgroup analysis of men 40 years or younger did not reveal any significant differences. Method of approach (anterior or posterior), type of mesh, and testicular status at the time of the repair had no significant impact on the answers to the questionnaire. We have recently repeated the calculations where we primarily used the t-test for unpaired data. When using the t-test for paired data we did not get any different significant differences.

Table V. Describing the outcome of the first two questions. There were no significant differences between the three groups.

	Operated bilaterally with mesh		**Operated bilaterally without mesh**		**Controls from the general population**	
	Positive responses/ Total number of responders	% (95% confidence interval)	Positive responses/ Total number of responders	% (95% confidence interval)	Positive responses/ Total number of responders	% (95% confidence interval)
1. Have you had a period of at least one year of involuntary childlessness during the last five years?	15/232	6.5 (3.3-9.6)	10/111	9.0 (3.7-14.3)	14/201	7.0 (3.4-10.5)
2. Have you undergone investigation for infertility the last five years?	6/229	2.6 (0.6-4.7)	5/112	4.5 (0.6-8.3)	9/201	4.5 (1.6-7.3)

Table VI. Describing the outcome of question 3-8. There were no significant differences between the two groups.

	Operated bilaterally with mesh		**Operated bilaterally without mesh**	
	Positive responses/ Total number of responders	% (95% confidence interval)	Positive responses/ Total number of responders	% (95% confidence interval)
3. Did you have any children prior to the hernia repair?	120/228	52.6 (46.2-59.1)	61/111	55.0 (45.7-64.2)
4. Did you have a period of at least one year of involuntary childlessness prior to the hernia repair?	14/229	6.1 (3.0-9.2)	6/110	5.5 (1.2-9.7)
5. Have you made any attempts to have children after the hernia repair?	58/230	25.2 (19.6-30.8)	31/112	27.7 (19.4-36.0)
6. Have you had a period of at least one year of involuntary childlessness after the hernia repair?	58/230	25.2 (19.6-30.8)	31/112	27.7 (19.4-36.0)
7. Have you undergone investigation for infertility after the hernia repair?	3/89	3.4 (0.0-7.1)	4/48	8.3 (0.5-16.2)
	Total number of responders	Mean number of children ± standard deviation	Total number of responders	Mean number of children ± standard deviation
8. How many children have you had after the last hernia repair?	91	0.9 ± 0.9	46	0.8 ± 0.7

Table V-VI includes the data from Table I in publication 3. The table is now redesigned and divided in two parts due to the need of more space in the smaller format of the thesis. Reprinted with permission © 2011 Mosby, Inc.

Study 4 (mesh/infertility: the retrospective study)

Altogether 42,775 repairs in 34,267 men born between 1950 and 1989 were identified in the Swedish Hernia Register (SHR) between 1992 and 2007 (Table VII). 233 of these men were also identified, according to the Swedish National Patient Register, with a diagnosis of "male infertility" (ICD code N46.9) registered the year after the first hernia repair and any time thereafter (Table VII).

Analyse A: Cumulative incidence of infertility in men operated for groin hernia versus the general population

Observed and expected cumulative incidences of infertility are presented in Table VII and Figure 6. None of the groups had an observed cumulative incidence of infertility greater than the expected cumulative incidence. For most groups, the cumulative incidence was even lower than that of the general population.

Analyse B: Mesh versus non-mesh repair and risk for infertility

In a multivariate logistic analysis of men operated bilaterally, with infertility as the dependent variable and adjusted for age and year elapsed since the repair, a significant difference was seen between men operated with mesh and men operated with suture repair (p=0.030). There was a higher risk for infertility in men who had undergone bilateral hernia repair with mesh on one or both sides.

In a corresponding multivariate logistic analysis of men operated unilaterally, mesh repair was not found to be significantly associated with an increased risk for infertility (p=0.082).

Table VII. Observed and expected cumulative incidences of infertility. Numbers are based on men born between 1950 and 1989 (N=34,267)

Group	**Number of men in the hernia register**	**Number of men diagnosed with infertility after the first registered hernia repair**	**Observed cumulative incidence (%, 95% confidence interval)**	**Expected cumulative incidence (%)**
Operated unilaterally without mesh*	6281	57	0.91 (0.67-1.14)	1.03
Operated unilaterally with mesh*	22420	133	0.59 (0.49-0.69)	0.67
Operated bilaterally without mesh*	226	0	0**	1.01
Operated bilaterally, mesh on one side*	346	3	0.87 (0-18.4)	1.05
Operated bilaterally, mesh on both sides*	2293	19	0.83 (0.46-1.20)	0.64
Repeated repairs on any side	2701	21	0.78 (0.45-1.11)	0.68

* No repeated repair on any side** Confidence interval not applicable

This is the data from the table in publication 4. The table is now redesigned due to the need of more space in the smaller format of the thesis. Reprinted with permission.

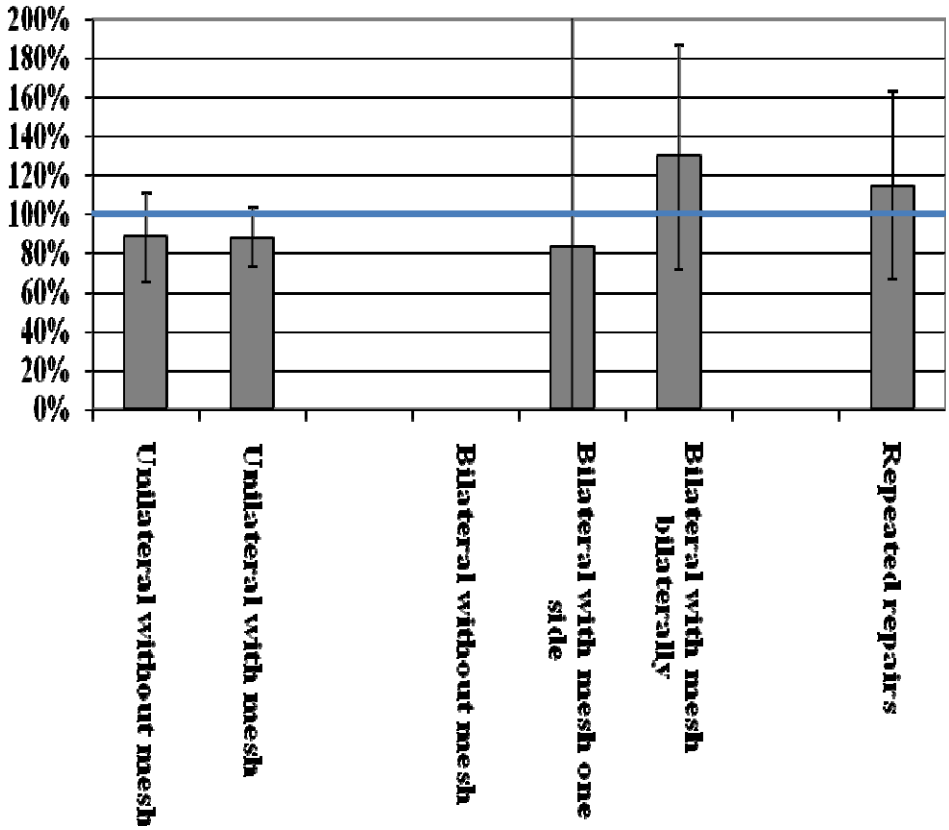

Figure 6 illustrating study 4 analyse A. Observed rates of infertility adjusted for expected rates. The thick line (100%) represents the expected infertility rate. None of the groups has an observed infertility rate that is significantly different from the expected. Reprinted with permission. © 2012 Mosby, Inc.

Discussion study 1 and 2

Sick-leave and postoperative pain

Since many of the patients who undergo operations for hernia are of working age, the treatment of inguinal hernia is not only of importance for the individual but also has great socioeconomic impact. Laparoscopic techniques for inguinal hernia were introduced in order to facilitate patient recovery and return to their daily occupation, while Lichtenstein was mainly introduced because of the low recurrence rate.

Both study groups had a low postoperative consumption of analgesics. TEP-patients consumed half as much as those with a Lichtenstein repair. If we assume that the patients used the highest allowed dose of analgesics, the Lichtenstein repair patients used the analgesics for no more than three days. This observation indicates that postoperative pain was not a big problem. We found that the TEP-patients had a shorter sick leave, especially those with manual labour. This result has been repeated many times by others[99-101] and nowadays the opinion of many surgeons is that TEP is preferable to those who are of working age, especially those with manual labour[102,103]. The main problem preventing TEP from being the dominating method is that it needs an experienced TEP surgeon otherwise the good results decreases[38].

The fact that all patients were informed that they could rely on the strength of the repair, in combination with the low use of analgesics, can raise the question of why the patients did not have an even shorter sick-leave. We think that the number of days on sick-leave was partly based on the patient's total experience of his operation, including his expectations and visual observation of the size of the bandages.

Since 2007 the Swedish Social Insurance Agency recommends a postoperative sick-leave of less than seven days for those who has not got manual labour. For those who have manual labour a maximum of two weeks is recommended for those operated with TEP and for those operated with Lichtenstein another third week is allowed without the doctor having to motivate it specifically.

Operation time

When performing the hernia repairs the surgeons were not as experienced in either of the techniques as the hernia specialists of today. This can be illustrated by the operating time. Our mean operation times for TEP and Lichtenstein were 81 and 59 minutes respectively. This can be compared to the shorter operation times in a newly published RCT (54 versus 49 minutes)[103]. Does this mean that the quality of the repairs is not comparable with modern standards? The overall results, especially the fact that the recurrence rates are in accordance with modern Swedish results, strongly suggest that the quality of the repairs in the study are good.

Technique specific complications

One serious technique specific complication (small bowel obstruction) was noted in the TEP-group. The endoscopic techniques, especially TAPP, are well known to have rare, technique specific and sometimes serious complications. Severe complications with low incidence are, however, better shown in larger studies or meta-analyses. Those complications mainly occur in the learning curve period[38]. Since many of today's TEP-surgeons are experienced, this is not a problem that should prevent them from doing TEP.

Recurrences

In Sweden the cumulative reoperation incidence after five years has decreased to around 3% (mostly Lichtenstein operations). This is mainly due to the increased use of mesh and perhaps also surgical specialization. It is often difficult to compare numerical results from different studies but the recurrence rates in our RCT seem to be normal and comparable with others.

The large Swedish randomized multicentre trial (SMIL II) comparing TEP and Lichtenstein included clinical examination after median 5.1 year on 1275 patients[99,104-106]. Although their primary endpoint (recurrence rate after five years) was not identical to ours, the studies are comparable. The SMIL II study recurrence rate[106] was almost the same in the TEP group (3.5% versus 4.3%) but lower in the Lichtenstein group (1.2% versus 5.1%). The higher recurrence rate in our

Lichtenstein group can probably not only be explained by the longer follow-up time. The main difference between the studies, apart from the number of patients and the years of its performance, is the fact that in the SMIL II study the two different operations were not performed by the same surgeons, which was the case in our study.

The question of long term recurrence after four years or more was meticulously discussed in the EHS guideline from 2009[38]. Lichtenstein was compared to both TEP and TAPP and there were no differences. On the other hand the included studies were of different designs and at least one was performed on recurrences[107]. The authors of the guideline did not wish to make a firm statement on the question of recurrence. In a newly published meta-analyse the authors stated that TEP was associated with more recurrences than open hernia repair but the group of open repair consisted of more than just Lichtenstein operations and also other than long-term studies were included[108]. In a newly published RCT, on TEP versus Lichtenstein, including both primary and some recurrent inguinal hernias, there was no significant difference in recurrences after five years[101] and the recurrence rates were quite similar to ours. When summarizing the meta-analyse[108], the guideline[38] and the new RCT[101], there seems to be no major difference in recurrence rates between TEP and Lichtenstein. The fact that we are not sure after almost 20 years of studies also indicates that the difference in recurrences is probably minor.

At least two reports on the long-term results of TEP after 10 years or more have been published during the last years[109,110]. These two studies included primary and recurrent hernias. The first study[109] with 13 years follow up had 8.9% recurrences for primary hernias and 10.8% for recurrent hernias. Half of the recurrences were asymptomatic and found at the clinical examination. The second study[110] had a ten year follow up and the recurrence rates were 4% and 11% respectively. Also in the latter asymptomatic recurrences were identified. In these two studies the follow up rates were lower than in our study. That is partly explained by more deaths after longer time but also by a higher rate of patients that were lost to follow up.

In general, RCT:s are considered to provide the best scientific evidence. The fact that the recurrence rates are known to increase with time[110] in combination with the practical difficulties in performing really long-term RCT:s have resulted in some authors considering other outcome measures that are not as time dependent to be more valuable[55]. The view of the twentieth century (1890-1990) which implies that the recurrence rate is the sole criterion of a good repair method is questioned more often lately[111].

Impaired sensibility, chronic pain and patient satisfaction

The finding of a higher frequency of impaired inguinal sensibility in the open group was expected and obvious already after one year and remained in the long term follow-up. This result is repeatedly found in many studies.

The frequency of persistent severe chronic pain was low, although two patients had been reoperated due to chronic pain. Only one patient reported daily use of analgesics. The impact on day-to-day life was minimal and around 92% reported complete recovery.

Chronic pain has gained increased attention as a major outcome measure in hernia surgery. It is defined as pain for more than three months[112] although there has recently been a suggestion of change in the definition of postoperative inguinal pain[58]. The suggestion is that pain for more than 6 months after hernia surgery should be regarded as chronic pain[58]. It is, however, difficult to compare different long-term studies on this topic because of methodological diversity and variation in the definitions[38]. The origin of the pain studied and its intensity is also sometimes difficult to find out[38].

In our studies, the proportion of patients with reported testicular pain was higher in the TEP group both in the immediate postoperative time and at long-term follow-up. We do not know the reason why this condition was more common after TEP. It may be related to a dissecting trauma to the main trunk of the genitofemoral nerve or the preperitoneal segment of its genital branch both of which are located preperitoneal without fascial cover[58]. It can also be a result of an inflammatory response to the mesh which is in direct contact with this nerve and its branches[58]. Long-term testicular pain is not a term that covers all sorts of postherniorrhaphy chronic pain. In a newly published guideline where the literature was reviewed and papers on this subject graduated according to the Oxford hierarchy of evidence, the conclusion was that chronic pain is lower after endoscopic hernia repair than after open techniques[52]. This statement indicates that our finding on this topic may not be representative for the world of TEP in general.

Costs

The TEP technique was more expensive in terms of hospital costs. About half the excess in direct cost for the TEP group compared with the open group was from disposables, and the other half was caused by a longer operation time. However, the indirect cost (from sick leave) counterbalanced the difference between the two groups. The shorter operation time and the use of more reusable instruments nowadays have probably lowered the costs at many clinics. Anyway, the hospital cost for TEP is still

considered to be higher than for Lichtenstein[38], but just as in our study the indirect costs are lower making the total costs equal[38].

One problem still has to be considered, at least in Sweden. The cost of the operation is paid mainly by the government and the cost for the sick leave is paid by the employer at least for the first two weeks. That means the employer and possibly the patient prefer a TEP but the hospital minimizes its costs when a Lichtenstein repair is performed.

Changes and improvements over time

Study 1, comparing the two tension-free mesh procedures TEP and Lichtenstein were among the first prospective randomized trials that addressed this issue. Both repair methods were quite new to most Swedish surgeons. Since then these surgical repair methods have undergone further development.

Materials have improved continuously. For the repair the lightweight large-pore mesh has been developed and is nowadays preferred by many surgeons, as it gives the patient less foreign body sensation without increasing the recurrence rate. According to three newly published meta-analyses this is the current opinion at least for the Lichtenstein repair[113-115]. For laparoscopic repair so far there seems to be no difference in long-term discomfort and no difference in recurrence rate[116]. Regarding the question if chronic pain is less common after lightweight mesh repair, the opinion is partly divided. The meta-analyse on laparoscopic repair stated there was no difference[116]. The three meta-analyses on Lichtenstein repair[113-115] showed different results although analysing almost the same studies. Two of them stated that lightweight mesh decreased the incidence of chronic pain[113,114] but the third stated there was no difference[115]. Finally, yet another new meta-analyse on studies of both Lichtenstein and laparoscopic repair stated that lightweight mesh reduces chronic pain[117].

The TEP technique used in our first study and the recommended technique of today differ in several ways. Tacks, staples or anchors for fixation of the mesh are used more seldom, especially if the hernia opening is not too large (< 3 cm). No fixation or fixation by fibrin glue is nowadays recommended because it is probably associated with less postoperative and chronic pain, less cost and still comparable recurrence rate[52]. The mesh size that we used in study 1 is still recommended if the hernia is not too large[38,52]. Some surgeons prefer even larger meshes like 15x15 cm or preformed meshes. Many of the surgeons performing the TEP repair today are very experienced in endoscopic techniques whereas the Lichtenstein repair is learned by almost all young surgeons and used at least occasionally by most surgeons performing hernia repairs in adults.

Lichtenstein's successor Amid has modified the method[37]. He still follows most of the originally described technique[35] but in selected cases he accepts the removal of a large indirect hernia sac and narrowing of the internal ring[37]. There has been a debate among Swedish surgeons on whether to follow the original method or to include the modification suggested by Amid as well as other modifications. Some surgeons still use the original method with or without the modifications and some also close the direct hernia opening in the transverse fascia. Closing the inner opening makes the posterior wall of the inguinal channel flatter until the mesh has been fixated to it by the healing process and it also prevents the mesh from getting adherent to the peritoneum. It can also counteract an early hernia formation between the transverse fascia and the mesh[118,119]. This part of a hernia repair is not in accordance with the original description, since it can add some tension to the repaired posterior wall. It is still debated whether it is the mesh or the lack of tension that is the most important part of the Lichtenstein repair. Another problem is that the published results from the Lichtenstein clinic with almost no recurrences despite a very large number of patients have not been replicated by other clinics.

Consequently, the methodological differences between the Lichtenstein repair technique used in our study and the technique of today varies depending on which technique is preferred by the particular surgeon nowadays.

One can discuss if the results of a study like ours is still of value despite the fact that it is quite old. In my opinion the age of the study is a minor problem if the design of the study is in accordance with modern principles. In the recently published RCT with almost similar primary and secondary outcomes the results were mainly the same[101].

Strengths and weaknesses of study 1 and 2

Lightweight mesh was not used in our study. Hence, if we had used lightweight mesh in our study, the result in the Lichtenstein group could perhaps have been improved with less long-term discomfort. However, the number of patients in the study was probably too small for us to expect a great influence on the result if we had been able to use lightweight mesh.

The prospective randomized long-term follow-up study was one of the first published studies on this subject, mainly due to the fact that its predecessor i.e. study 1 was initiated and finished early in the modern hernia era. The median follow-up time of 7.3 years is still among the longest. In total these two studies have been cited in 73 publications. The fact that this figure includes two meta-analyses of RCTs[108,120] and one EHS guideline[38] further strengthen the studies.

A possible weakness of the two studies, in terms of interpreting the results, was that they included both primary and recurrent hernias. Further more patients with

bilateral primary hernias were included. However, given the small number of recurrent hernias as well as bilateral hernias, these inclusions probably have only slightly clouded the data. The TEP group had many similarities with the patients referred to in the two previously mentioned long-term follow up studies of laparoscopic hernia surgery, of ten years or more.[109,110].

Some major strengths of the studies were the high follow-up rate and the fact that they were based on both questionnaires and the clinical follow-up with a physical examination. The latter was carried out by the same independent observer (MH) both after one year and at the long-term follow-up. The observer did not participate in the hernia operations and had no personal interest in the results other than making the follow-up observations as objective as possible. There was no analysing of the follow-up data until all data were collected.

The immediate contact with the physician strengthens the conclusions in a way that could not have been achieved by a questionnaire follow-up, no matter which statistical methods had been used, in particular by assessing the severity of symptoms in a way that would be impossible with questionnaires. The answers in our questionnaires were not consistently complying with the findings at the physical examinations. Our finding that clinical examination and questionnaire can generate different answers on the same questions is in accordance with the findings in two other studies[121,122].

Regarding the statistical methods used in the two studies, they are not exactly the same. In study 2 we did not use the unpaired t-test. The reason for this was mainly based on a recommendation from the editor of the journal in which the paper was published. However, using either parametric or nonparametric tests did not alter the results.

TEP or Lichtenstein?

Our two studies support the concept of individualizing inguinal hernia repair for the best results and cost effectiveness. For instance, TEP is an excellent method for individuals of working age with primary hernias (1-sided or bilateral) who require a short convalescence. This is more pronounced for those who have manual labour. Moreover it is beneficial for a recurrent hernia repair after a previous anterior approach repair, since exploration of previously operated tissues is avoided. In this context, however, it is also important to take into account the experience of the clinic and the surgeon regarding a specific technique. On the other hand, according to the Swedish Hernia Register, the Lichtenstein technique has provided excellent results although performed by many surgeons not specialized in hernia surgery. Furthermore, the Lichtenstein repair is often performed under local anesthesia, which may be technically challenging but avoids the hazards of general anaesthesia and spinal

anaesthesia. This is difficult although possible for TEP. Since many hernia patients are old and have other complicating diseases that makes local anesthesia preferable there will always be a place for the Lichtenstein repair. Finally the patients' preferences must be taken into account.

A comparison table between our results in study 1 and 2 and those referred to in two modern guidelines from the hernia societies[38,52] (EHS and IEHS) is shown in table VIII.

Overall, in our two studies, both the TEP group and the Lichtenstein group were associated with good short- and long-term results and with high reported rates of complete recovery.

Table VIII. Our results compared to the statements of two modern guidelines[38,52]. These are: European Hernia Society guidelines in the treatment of inguinal hernia in adult patients[38] and Guidelines for laparoscopic (TAPP) and endoscopic (TEP) treatment of inguinal Hernia [International Endohernia Society (IEHS)] [52].
The long-term results from study 2 were included in the basic data of the guidelines. The definition of the levels (1-4) is from the Oxford Centre for Evidence-Based Medicine. Level 1A is the best.

Our results on TEP versus Lichtenstein	**Conclusions from guidelines**	**Levels of evidence**
TEP has longer operation time	The same	1A
TEP-patients consume less postoperative analgesics	The same	1A
TEP results in shorter sick-leave	The same	1A
TEP results in earlier return to normal activities	The same	1A
TEP results in fewer hematomas	The same	1A
TEP results in less chronic numbness	The same	1B
TEP results in higher hospital costs	The same	1B
TEP results in lower socioeconomic costs	The same	1B
TEP results in a higher incidence of testicular pain	Do not agree	No level stated
Chronic groin pain becomes equ-al in the long term perspective	The same	1B
Long-term recurrence rate is equal	The same	1A
One year satisfaction is equal	Not precisely commented	
Subjective long-term recovery is equal	Not precisely commented	

Discussion study 3 and 4

Infertility after inguinal hernia mesh repair – is this really a problem?

Study 3 and 4 were not designed to determine whether inguinal hernia surgery in males increases the risk of infertility per se, but rather to explore the effect of the mesh on the fertility. Our two studies were designed to adjust for confounding factors. This seemed important since infertility has many etiologies involving both partners. In study 3, it was our intention to have study groups that were as identical as possible except for the method of repair i.e. mesh or not mesh. Since hernia operations with or without mesh are not performed in exactly the same way, it is not possible to rule out that the operation techniques by themselves could have influenced the results. We also used control groups from the normal population, something which made it possible to determine whether the outcome differed from the background population.

Some previous studies had suggested that mesh used in male inguinal hernia repair could cause infertility through obstruction of the structures of the spermatic cord. Our aim was to explore this theory further. We used involuntary childlessness and diagnosed male infertility as surrogates for the incidence of obstruction. The number of human studies in this field is still limited and most of them have used surrogates as sperm quality, hormone levels and physiology of the testis.

A more direct, distinct and reliable way of studying a possible increase in infertility after mesh repair would have been to perform spermiogram and when necessary vasography and testicular biopsy. Most certainly, it would have been impossible to find enough men who would have accepted to be included in such an intimate study.

The operated men in study 3 represent a group that hypothetically runs the greatest risk of infertility, if the use of mesh has a substantial impact on the risk of obstruction of the structures of the spermatic cord. Since no increased risk was seen after bilateral mesh repair, we assumed that unilateral use of mesh should be even safer as far as infertility was concerned. This was also in accordance with the result of analyse A in study 4, where we separately compared the expected and cumulated incidences in unilaterally as well as in bilaterally operated men (with and without mesh).

Study 3 could have benefitted from larger study groups. The identified group of men bilaterally operated without mesh was limited, even though all such operations recorded in the register were included. This limited the inclusion of men in the other two groups. The Swedish Hernia Register is the largest hernia register in the world, comparable only to the Danish Hernia register. Thus we find it hard to believe that it is possible to repeat the study including even more patients operated bilaterally without mesh. This sets the limit.

A higher response rate than 60 % would also have been preferable. The somewhat low response rate is very well explained by the personal and intimate questions in the questionnaire and was not unexpected. This is well illustrated by the two Danish register studies on sexual problems after inguinal hernia repair, were the response rates were just slightly higher (68%)[59,60].

In study 4 the cumulative incidences of infertility in all studied groups were low and not statistically different from the expected ones. We do not know the true incidence since the rates are only based on men seeking health care because of infertility. There may have been many more infertile men in the study group, as well as in the control population, without the desire to have children and thus never being diagnosed as infertile.

In study 4 the multivariate logistic analysis of men operated bilaterally showed a small but significant difference between men operated with mesh and men operated with suture repair. There was a higher risk of infertility in men who had undergone mesh repair. Whereas this last analyse suggests an increased risk of infertility due to mesh repairs, the clinical importance of this increase remains questionable. Since the incidences of diagnosed infertility were very low in all groups, a small potential increase in any of the groups is so low that it lacks clinical relevance. Thereby we think that from a clinical point of view the results of the multivariate logistic analyses are in accordance with our earlier results (study 3 and 4A).

Returning to outdated non-mesh methods would most likely lead to an unwanted increase in recurrences and more reoperations. A reoperation may be even more traumatic to the spermatic cord than any primary repair, with or without mesh. Other complications are also supposed to occur more often, if the recurrence rates and thereby the frequency of reoperations increases. This is not the way to go.

We believe that these two retrospective and prospective studies based on register data, provide strong evidence that inguinal hernia surgery using mesh does not cause any clinically important risk of male infertility. Surgery for male inguinal hernia using mesh techniques may continue to be performed without major concern about the risk of male infertility. The experts' opinion that the mesh methods are the methods of choice is strengthened by our findings[38].

Recently two additional animal[123,124] and five more human[125-129] studies at least partly on this subject have been published. The conclusions of the first three human studies[125-127] are in accordance with ours. The fourth study[128] compared the use of light and heavy weight mesh in TEP operations. That study found impaired sperm motility after bilateral TEP with light weight mesh but the study was not designed to

determine whether it had any clinical significance regarding the fertility. The result of that study do not strengthen the by other proposed theory that mesh is a fertility problem due to the inflammatory reaction and the resulting fibrosis. Anyway, our prospective study showed no difference on involuntary childlessness when comparing light and heavyweight mesh. The fifth study[129] compared the testicular volume, blood flow and hormones after laparoscopic and Lichtenstein repair and found that the testicular functions were better preserved after laparoscopic repair. The study did not compare mesh and no mesh and conclusions on the role of mesh can not be drawn from that study. The conclusions of the two not identical animal studies[123,124] diverge. A recently published review article concluded that, although several animal studies have shown substantial mesh effects on the structures of the spermatic cord, it does not seem to have a clinical impact on male fertility in men who undergo inguinal hernia mesh repairs[130]. The adequacy of using small animals in anatomical studies of mesh related hernia problems have also been questioned[53]. Finally, an invited commentary (male) accompanying one of the last published papers on this subject[125] stated that there is no such problem as mesh-induced obstructive azoospermia[131]. He also thought that the so called problem is hyped by modern American media, trying to make us think that we are forever young and it is never too late to have another child[131]. At least two more studies on this subject are on their way[130,132].

Conclusions

TEP and Lichtenstein inguinal hernia repairs are comparable mesh techniques with overall good short-term results. TEP is associated with less postoperative pain, shorter recovery and sick leave, less hematomas, less impaired inguinal sensibility, longer operation time and higher hospital costs.

The long-term results of the TEP and Lichtenstein inguinal hernia repairs are good, with a high patient satisfaction rate, almost no impact on day-to-day life and a low frequency of persistent severe chronic pain. TEP continues to be associated with less impaired inguinal sensibility. The finding that TEP results in more testicular pain must be questioned since that finding has not been repeated by others.

Bilateral inguinal hernia mesh repairs in men do not increase the frequency of involuntary childlessness.

Inguinal hernia mesh repair is not associated with a clinically important risk of male infertility. The mesh repair techniques can continue to be the methods of choice even in young men.

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Errata

1. In publication 1, table III, the column titles have been mixed in the final edition. This version has the correct column titles (type of work changed to daily occupation and laparoscopic changed to TEP):

	Days on sick leave*			Days to complete recovery*		
Daily occupation	**Lichtenstein**	**TEP**	**p value**	**Lichenstein**	**TEP**	**P value**
Manual labour	16±10	11±4	0.003	30±12	17±10	0.001
Mixed	10±5	8±5	0.08	13±10	13±11	0.98
Office	7±6	5±4	0.12	15±10	10±8	0.04
Retired	-	-	-	20±16	20±14	0.98
All	11±8	8±5	0.003	19±13	13±10	0.007

* Mean value ± SD

2. In publication 1 “with” anesthesia should be under anesthesia.

3. In publication 2 on page 315 “orchiectomy” should be orchidectomy.

4. In publication 3 the reference nr 1 should be: Am J Surg 1989; 157(2): 188-93.

5. In publication 4 the sentence about short learning curve should only refer to the Lichtenstein repair.

6. In publication 4 the reference nr 7 should be as follows: Surg Endosc 2010; 24: 455-61.

7. In publication 4 the power analysis was made in retrospective and since that the information cannot be used the way we did.

8. In publications 3 and 4 the term obstructive azoospermia was frequently used. After publishing those two papers I have learned that the term obstructive azoospermia should only be used when there is an obstruction or an absence of the vas deferens. When there is an obstruction of the artery/veins in the spermatic cord this causes azoospermia by testicular failure and should not be termed obstructive azoospermia. Anyway, this does not change the message of the two publications.

Populärvetenskaplig sammanfattning

Med stigande ålder försvagas våra vävnader. Om bukväggen i ljumsken blir för svag, så kan bukinnehållet pressas ut genom svagheten. Detta kallas för ljumskbråck. Sjukdomen är mycket vanligare hos män och drabbar alla åldrar. Ju äldre man är, desto vanligare att man drabbas av ett ljumskbråck. Man upplever då, framför allt vid ansträngning, en oftast rörlig och ibland smärtande knöl i ljumsken. Symtomen för personen till läkare som då oftast rekommenderar operation. Någon annan bra behandling finns inte.

Operation för ljumskbråck är det allra vanligaste kirurgiska ingreppet i västvärlden. Bara i Sverige görs 16,000 ljumskbråcksoperationer per år. Så gott som alla operationer registreras i Svenskt Bråckregister. Registret används för att säkerställa och förbättra kvaliteten vid ljumskbråcksoperationer. Idag innehåller registret fakta om mer än 200,000 operationer.

Den kirurgiska tekniken vid ljumskbråcksoperationer har förbättrats under de senaste 130 åren. En mängd olika metoder har utvecklats. De första 100 åren åtgärdades bråcken oftast med en suturplastik. Svagheten åtgärdades då genom att man sydde över närliggande muskler och muskelhinnor. Resultaten var oftast inte speciellt bra och i medeltal var fjärde patient fick med tiden ett nytt bråck i samma ljumske, ett så kallat recidiv. Operation för recidiv är kirurgiskt svårare.

De sista 25 åren har man i gradvis ökad omfattning övergått till att använda ett nät av plast vid ljumskbråcksoperation. Istället för att reparera svagheten så låter man nätet täcka över densamma. Fördelarna med nätoperation har visat sig vara många. Framför allt har antalet recidiv minskat och dessutom så medför användandet av nät mindre spänning i operationsområdet och därmed mindre postoperativ smärta och snabbare återhämtning. Öppen spänningsfri operation med nät är idag den vanligaste metoden.

De senaste 20 åren har också titthålsteknik använts för att åtgärda bråck, även då använder man nät. Titthålsoperationerna kan utföras på flera olika sätt där den vanligaste kallas TEP.

De två första studierna som beskrivs i denna avhandling jämförde resultaten mellan öppen nätoperation och titthålsoperation med nät (TEP). Den första studien innefattade resultaten efter ett år och den andra redovisade resultaten efter cirka 7 år.

Vi fann att de båda operationsmetoderna gav relativt få recidiv. Titthålsoperationens fördelar var mindre smärta efter operationen, kortare sjukskrivning, snabbare återhämtning och mindre ofta nedsatt känsel i huden vid operationsområdet. Den öppna operationen hade fördelarna att den var billigare, snabbare och gav mindre problem med smärta i testikeln på den opererade sidan. Frånsett skillnaderna i nedsatt känsel och testikelsmärta så jämnade resultaten ut sig i det långa loppet. Våra resultat stämmer väl med andra liknande studier, frånsett att andra studier inte har påvisat mer testikelsmärta efter titthålsoperation.

Vår slutsats är att båda operationsmetoderna är bra och har olika fördelar. Den man som behöver en operation bör därför erbjudas den metod som ger mest fördelar i just hans fall. Slutsatsen gäller inte för kvinnor eftersom de oftare har en annan typ av bråck, vilket kräver andra överväganden.

Hos män passerar sädessträngen precis i området där bråcket brukar vara. Djurstudier och ett litet antal fallbeskrivningar har gjort att vissa forskare misstänkt att nätet kan orsaka en skrumpning av sädessträngen. Detta skulle i så fall kunna leda till att spermierna blir sämre eller inte kan passera ut. De har därför varnat för operation med nät framför allt på yngre män. Risken har bedömts som störst vid operation i båda ljumskarna.

I den tredje studien har vi med hjälp av det Svenska Bråckregistret studerat män som bråckopererats i båda ljumskarna med nät eller helt utan nät. Dessa har jämförts med jämngamla män i normalbefolkningen. Vi har via ett frågeformulär undersökt om männen har upplevt eller utretts för ofrivillig barnlöshet. Vi fann inga säkerställda skillnader som talade för att nät skulle vara olämpligt.

I vårt land finns också ett patientregister där alla diagnoser i samband med sjukvårdsbesök registreras. I den fjärde studien har vi med hjälp av Bråckregistret och Patientregistret undersökt hur vanligt det är att bråckopererade män senare fått diagnosen manlig infertilitet (sterilitet). Resultatet har sedan jämförts med hur vanlig denna diagnos var hos alla svenska män i samma ålder. Vi fann att infertilitet var mycket ovanligt i alla grupper och att användandet av nät inte medförde någon ökning av betydelse.

Slutsatsen från de två sista studierna är att rädslan för infertilitet på grund av nätoperation har varit överdriven. Vi tycker att operation med nät har många fördelar och att man därför kan fortsätta att använda nät till alla vuxna män som behöver opereras för ljumskbråck.

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Paper I

Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: A prospective randomized controlled trial

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Background. *This study was designed to compare an open tension-free technique (Lichtenstein repair) with a laparoscopic totally extraperitoneal hernia repair (TEP).*
Methods. *One hundred sixty-eight men aged 30 to 65 years with primary or recurrent inguinal hernia were randomized to TEP or open mesh technique in the manner of Lichtenstein. Follow-up was after 1 and 6 weeks, and 1 year.*
Results. *Eighty-one patients were randomized to TEP, and 87 to open repair. For 1 patient in each group, the operation was converted to a different type of repair. No difference was seen in overall complications between the 2 groups. However, 1 patient in the TEP group underwent operation for small bowel obstruction after surgery. A higher frequency of postoperative hematomas was seen in the open group (*$P < .05$*). Patients in the TEP group consumed less analgesic after surgery (*$P < .001$*), returned to work earlier (*$P < .01$*), and had a shorter time to full recovery (*$P < .01$*). Two recurrences occurred in the TEP group 1 year after surgery.*
Conclusion. *The TEP technique was associated with less postoperative pain, a shorter time to full recovery, and an earlier return to work compared with the open tension-free repair. No difference was seen in overall complications. However, 2 recurrences did occur after 1 year in the TEP group. (Surgery 2003;133:464-72.)*

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LAPAROSCOPIC TECHNIQUES FOR inguinal hernia have been introduced in an attempt to reduce hernia recurrence and facilitate patient recovery and return to work. Several studies comparing laparoscopic hernia repair with a variety of open conventional hernia repairs[1-10] and open tension-free mesh techniques[11-15] have been published. Laparoscopic repairs have been associated with less postoperative pain and a more rapid return to normal activities.[10,16] These advantages have been more apparent when laparoscopic repairs have been compared with sutured repairs rather than tension-free repairs.[16]

Still, the place of laparoscopic inguinal hernia repair remains controversial because of technical complexity, serious complications, including visceral and vascular injuries, and longer operation time.[10] However, the serious complications that have been described have all followed the transabdominal preperitoneal laparoscopic (TAPP) inguinal repair technique. In an attempt to reduce the risk for intraabdominal complications, a totally extraperitoneal endoscopic technique (TEP) has been introduced.[17-21] Among open tension-free techniques, the Lichtenstein procedure has gradually evolved as the gold standard because it has shown acceptable morbidity and appreciable reductions in postoperative discomfort and recurrence rate.[22,23]

So far, only two randomized studies have been published that compare the TEP technique with an open tension-free mesh technique like the Lichtenstein technique.[24,25] In these studies, some advantages for the endoscopic operation in terms of postoperative pain, hospital stay, and return to normal life and work have been reported. These findings could be of importance because they sug-

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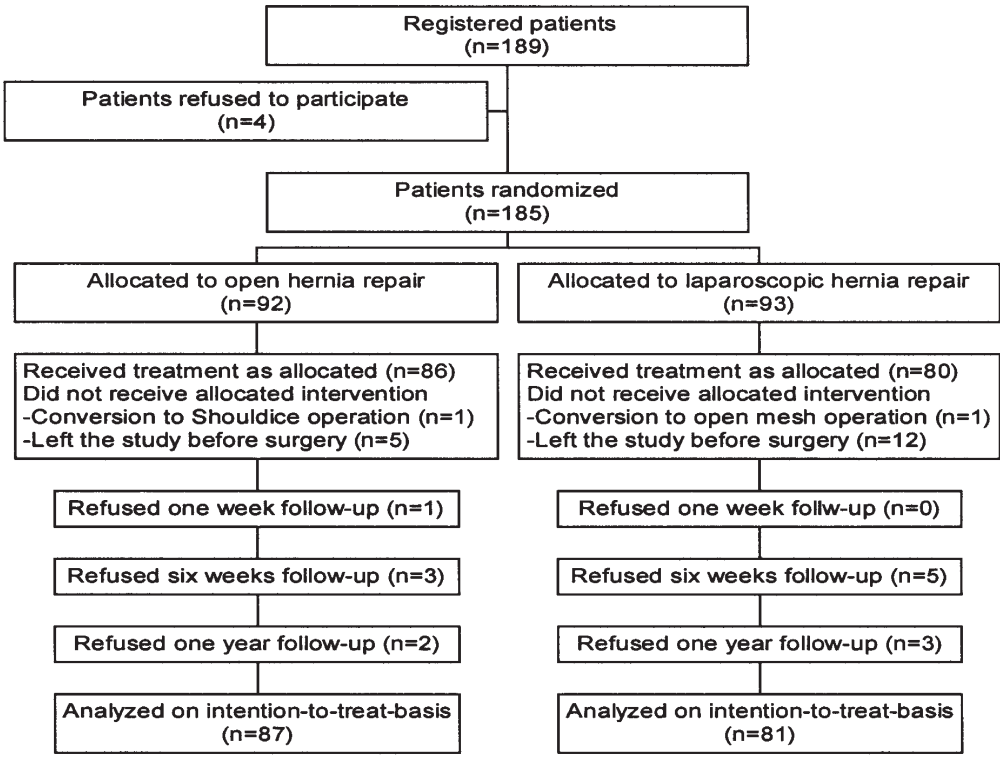

Fig 1. Flow diagram of study according to Consolidated Standards of Reporting Trials statement.

gest that the TEP technique could benefit the patient and the community.

This study was designed to compare an open tension-free technique (Lichtenstein repair) with a laparoscopic tension-free repair (TEP technique). We specifically focused on the impact of postoperative pain, estimated as analgesia requirement, and sick leave.

MATERIAL AND METHODS

Study population. Between 1996 and 1997, 185 men, aged 30 to 65 years, referred to the Department of Surgery, Lund University Hospital, Lund, Sweden, for primary or recurrent inguinal hernia repair were enrolled in the study after written and oral information. Informed consent was obtained in all patients. Excluded from the study were patients with irreducible hernia, ASA class 3 or 4, history of surgery to the lower abdomen (except inguinal hernia repair), acute abdominal disease, and coagulation disorder or ascites. Four eligible patients declined to undergo randomization.

After randomization, 17 patients were excluded from the study for various reasons: initially missed exclusion criteria (n = 4), patient request (n = 3), too long a preoperative waiting period (n = 3), and other (n = 7). No significant difference was seen in age, preoperative symptoms and signs, or type of work between these 17 patients and the 168 patients who were actually included in the study. The Ethical Committee of the Medical Faculty of Lund University approved the study.

Planned intervention. A flow chart summarizing the study is shown in Fig 1. During the outpatient visit, eligible patients were randomized to either total extraperitoneal laparoscopic hernia repair (TEP; study group)[17-21] or open tension-free repair according to Lichtenstein (control group).[22,23] Patients were randomized in blocks of 10 with sealed envelope. Surgery was performed by 3 of the authors (AB, PL, JW) with experience in laparo-

scopic surgery. The operations were performed as day surgical procedures. However, patients stayed overnight when necessary for medical reasons. In both groups of patients, prophylactic antibiotics, cefuroxime, were given intravenously. The TEP group also received a single dose low–molecular weight heparin subcutaneously (Klexane, 20 mg, Arentis Pharma, Stockholm, Sweden).

The TEP operation was performed with general anesthesia. An incision was made below the umbilicus, and the rectus sheath was incised. The preperitoneal space was opened with a dissecting balloon (OMS-PDB 1000, Origin, Calif). Through this incision, a blunt-tip (10-mm) trocar (OMS-T10BT, Origin) was introduced. Carbon dioxide was insufflated to a pressure of 10 to 12 mm Hg. In addition, 2 reusable 5-mm trocars were inserted in the midline below the initial trocar. The operation was then carried out with a 10-mm 0-degree or 30-degree endoscopic camera. A 10×15–cm polypropylene mesh (Marlex, C.R. Bard, Chelmsford, Mass) was used. The mesh was fixed to the abdominal wall and the ligament of Cooper with a screwstapler (OMS-TTS, Origin). The skin incisions were closed with 4/0 polyamid (Ethilon, Ethicon, Johnsson & Johnsson, Bryssel, Belgium).

In the control group, surgery was performed with an open tension-free mesh technique according to Lichtenstein.[22,23] A 10×15–cm polypropylene mesh (Marlex), which is somewhat larger than originally described by Lichtenstein et al,[22] was fashioned. The mesh was fixed to the abdominal wall with a 2/0 polypropylene suture according to the original description.[22,23] The externus oblique fascia was sutured with 3/0 polyglactin, and the skin incision was closed with 4/0 polyamid. The open procedure was performed with regional or general anesthesia, depending on anesthesiologic considerations or patient preference.

Evaluation of patients. Acetaminophen and dextropropoxyphene were used as postoperative analgesics. Furthermore, the patients were asked to complete a comprehensive questionnaire once daily during the first week and then weekly the following 5 weeks. The questionnaire included questions on complications, such as fever, local swelling, redness, and tenderness. Questions were also asked about how much the operation influenced the ability to carry out daily activities and the ability to move, end of sick leave, and time to complete recovery (ie, when the patients believed that they had quite recovered from the operation). Pain was estimated on a visual analogue scale, from painless to unbearable pain. The patients received thorough information regarding the specific items of the questionnaire by a research nurse. In addition, the patients were given instructions regarding self-medication with analgesics, which was allowed to a maximum of 4 g of acetaminophen and 400 mg of dextropropoxyphene per 24 hours. All patients were also informed that they could rely on the strength of the repair, and they were encouraged to return to unrestricted activity and work as soon as possible. A certificate of illness, which entitled the patients to receive sick pay for a maximum of 7 days was prescribed by the responsible surgeon and extended at the request of the patient for not more than 7 days at a time.

Follow-up was done at 1 and 6 weeks after surgery at the outpatient clinic by a research nurse, and at 1 year by an independent surgeon (MH). At the 1-week and 6-week follow-ups, the wound was inspected, analgesic consumption reported by the patient, complications (eg, urinary retention, constipation, hematoma, wound infection, seroma, hydrocele, neuralgia, testicular pain, pain from the wound, and impaired sensibility) noted, and the questionnaire collected. Furthermore, number of days on sick leave was noted. One year after the surgery, postoperative symptoms were registered. The scar was inspected. The inguinal area was examined, and impaired sensibility (defined as loss of the ability to register touch, an unpleasant sensation produced by normal touch, or the presence of numbness and tingling), indicating lesions of sensory nerves, was recorded. The presence of a recurrent hernia was based on clinical examination showing a palpable reducible lump in the treated groin or in clinically uncertain cases with herniography.

Calculations of costs were made for direct costs (different equipment, operation time, and hospital stay) and indirect costs (sick leave) to estimate the total health cost. The total health cost also included costs of the reoperation for a small bowel obstruction and estimated costs of rerepair of 2 recurrences. The operating room cost was $15.57 per anesthesia minute. The costs for disposable equipment and other materials in the TEP operation were: blunt-tip trocar, $112.86; dissecting balloon, $153.89; screwstapler, $197.78; camera-cable protection bag, $1.55; polypropylene mesh, $38.94; and 4/0 polyamid, $1.36. For the open repair, the costs were: polypropylene mesh, $38.94; polypropylene, $2.22; polyglactin, $2.47; and polyamid sutures, $1.36. The investment cost for the laparoscopic equipment was not considered. Hospital cost was $325.46 per night and $165.02 for day surgery. For indirect costs, the value of lost production for each day of sick leave was calculated with multiplying the average number of hours of

Table I. Age, work, and preoperative symptoms and signs for the patients included in the study

	Open repair group n = 87	*Laparoscopic repair group n = 81*	*P value*
Age (yrs)	49 ± 9	50 ± 9	0.42
Work (n)			
Labor work	22 (25)	21 (26)	0.92
Mixed work	27 (31)	29 (36)	0.51
Office work	32 (37)	25 (31)	0.42
Retired	5 (6)	6 (7)	0.66
On the sick list	1 (1)	0 (0)	0.99
Symptoms (n)			
Pain	52 (60)	45 (56)	0.58
Bulge	83 (95)	79 (98)	0.68
Incarceration	0 (0)	2 (2)	0.23
Analgesic requirement	2 (2)	2 (2)	0.99
Subgroups of hernia (n)			
Primary	69 (79)	61 (75)	0.54
Bilateral	3 (3)	7 (9)	0.20
Recurrent	15 (17)	13 (16)	0.84

Values in parentheses are percentages.

work in the population studied and labor cost per hour. The Swedish total labor cost per hour was $18.43 plus 67% in social costs ($1 = SEK 8.09; December 31, 1998).

Outcome measures. Primary outcome measures were pain after surgery, estimated as total consumption of analgesics, and number of days on sick leave. Secondary outcome measures were operation time, complications, time to complete recovery after surgery, recurrence of inguinal hernia, and costs.

Sample size. In a pilot study, we found that patients who underwent TEP surgery differed in analgesic consumption and number of days on sick leave compared with patients who underwent operation according to the Lichtenstein technique. Thus, with an α error of 0.05 (2-sided) and a power of 0.90, it was found that 70 patients in each arm would be sufficient to detect a difference in 12 days of sick leave in the open group and 8 days of sick leave in the TEP group. The previous calculated sample size would also, with an α error of 0.05 and a power of 0.92, detect a difference in acetaminophen consumption of 10.5 g in the open group and 6.5 g in the TEP group.

Statistical analysis. Analysis of outcome measures for the TEP group and the open group was done on an intention-to-treat basis. The results for continuous variables are presented as mean ± standard deviation, if not stated otherwise. For categoric data, absolute numbers in addition to percentages are given. For numeric data, differences between groups were analyzed with unpaired *t* test, except for data with skewed distribution of numbers, when the Mann-Whitney *U* test was used. The χ^2 test was used for categoric data, except when expected frequencies were less than 5, when Fisher exact test was used. A probability level of a random difference of *P* less than .05 was considered significant.

RESULTS

Of the 168 patients included in the study, 140 had primary hernia (including 10 bilateral cases) and 28 patients had recurrent hernia (Table I). Twenty patients had previously undergone hernia surgery contralaterally. Eighty-one patients were randomized to the laparoscopic group, and 87 to the open group. No significant difference was seen in age, preoperative symptom and signs, and type of work between the 2 groups of patients (Table I).

Perioperative complications are listed in Table II. Seven patients (9%) in the TEP group and 4 (5%) in the group with open repair had perioperative complications (P = .36). None of the 4 patients with epigastric artery bleeding needed blood transfusion. However, for 1 of them, a patient in the TEP group, the operation had to be converted to an open tension-free repair because of the bleeding. The 3 electrocardiographic or heart rhythm changes were all of temporary nature. In both cases of registered injury to the peritoneum, we were able to maintain the pressure of the pneumopreperitoneum and no conversion had to be undertaken. One patient had acute airway obstruction for unknown reason during an operation with general anesthesia. In the open group, 1 patient happened to have a small serosal

Table II. Complications and recurrences

	Open repair n = 87	*Laparoscopic repair n = 81*	*P value*
Perioperative Complications			
Epigastric artery bleeding yes/no	2/85	2*/79	0.99
ECG or heart rhythm change yes/no	1/86	2/79	0.61
Injury to peritoneum yes/no	-	2/79	-
Acute airways obstruction yes/no	0/87	1/80	0.48
Serosal tear in the colon yes/no	1†/86	0/81	0.99
Postoperative Complications			
Bowel obstruction yes/no	0/86	1‡/80	0.99
Urinary retention yes/no	2/84	4/77	0.43
Constipation yes/no	6/80	8/73	0.50
Hematoma yes/no	18/68	7/74	0.03
Wound infection yes/no	2/84	0/81	0.50
Seroma yes/no	2/84	0/81	0.50
Hydrocele yes/no	0/85	1/80	0.99
Neuralgia yes/no	4/81	5/76	0.74
Testicular pain yes/no	6/79	19/62	0.003
Pain yes/no	22/63	14/64	0.22
Impaired inguinal sensibility yes/no	38/47	8/71	<0.0001
Recurrence (one-year follow-up) yes/no	0/85	2/76	0.23

*One laparoscopic operation with perioperative bleeding was converted to open surgery ad modum Lichtenstein.
†A small serosal tear in the colon during an operation for a sliding hernia resulted in a Shouldice operation (to avoid mesh).
‡The patient was reoperated on three days postoperatively. The small bowel had herniated through a small hole created by mistake in the peritoneum during the laparoscopic hernia repair.

tear in the colon of a sliding hernia, which resulted in a hernia repair according to Shouldice (to avoid mesh). Except for the 2 patients with injury to the peritoneum, all the patients with perioperative complications stayed overnight for observation at the hospital (see subsequent).

A difference was seen in operating time in favor of the open technique. The operation time was 81 ± 27 minutes for the TEP group and 59 ± 20 minutes for the Lichtenstein group ($P < .001$).

The average hospital stay after surgery was 13.6 ± 6.9 hours in the TEP group and 12.4 ± 6.3 hours in the open group ($P = .24$). Sixty-three percent of the patients were discharged within 12 hours. Thirty-seven patients, 19 patients in the laparoscopic group and 18 in Lichtenstein group ($P = .95$), stayed overnight at the hospital for various reasons: perioperative epigastric artery bleeding (n = 4), perioperative electrocardiographic or heart rhythm change (n = 3), acute airway obstruction (n = 1), small preoperative serosal tear in the colon (n = 1), and postoperative discomfort consisting of different combinations of nausea, dizziness, fatigue, and pain (n = 29). The average hospital stay for these patients was 24 ± 4 hours. All patients were discharged within 30 hours. No difference was seen in hospital stay between patients who underwent operation according to Lichtenstein with regional or general anesthesia (data not shown). Furthermore, no difference was seen in hospital stay between patients who underwent TEP or open surgery with general anesthesia.

The follow-up rates were 99% (167/168) after 1 week, 95% (160/168) after 6 weeks, and 97% (163/168) after 1 year. At the follow-up 1 week after surgery, patients in the TEP group had consumed less analgesics than patients in the Lichtenstein repair group. In the laparoscopic group, patients had used a median of 5 g (range, 0 to 28 g) acetaminophen versus a median of 11 g (range, 0 to 28 g) acetaminophen in the open repair group ($P < .0001$, Mann-Whitney U test). For dextropropoxyphene, the corresponding figures were 400 mg (range, 0 to 2400 mg) in the TEP group versus 900 mg (range, 0 to 2800 mg) in the open group ($P < .0001$, Mann-Whitney U test).

The patients in the TEP group returned to work earlier than the patients in the open group (8 ± 5 days versus 11 ± 8 days; $P = .003$). This difference was more obvious in the subgroup of patients with labor work than among office workers (Table III). Patients in the laparoscopic group reported a shorter time to complete recovery than patients in the Lichtenstein group (13 ± 10 days versus 19 ± 13 days; $P = .007$; Table III).

All the postoperative complications reported by the patient or recorded by the research nurse and the surgeon at the follow-up in the outpatient clin-

Table III. Number of days on sick leave and time to complete recovery

	*Days to complete recovery**			*Type of work*		
*Days on sick leave**	*Lichtenstein*	*Laparoscopic*	*p-value*	*Lichenstein*	*Laparoscopic*	*p-value*
Manual labor	16 ± 10	11 ± 4	0.003	30 ± 12	17 ± 10	0.001
Mixed	10 ± 5	8 ± 5	0.08	13 ± 10	13 ± 11	0.98
Office	7 ± 6	5 ± 4	0.12	15 ± 10	10 ± 8	0.04
Retired	-	-	-	20 ± 16	20 ± 14	0.98
All	11 ± 8	8 ± 5	0.003	19 ± 13	13 ± 10	0.007

*Mean value ± SD

ic are shown in Table II. One patient who underwent operation with the TEP technique had a postoperative hydrocele develop. Still another patient in this group was admitted to the hospital and underwent reoperation 3 days after surgery for small bowel obstruction. At the reoperation, the small bowel was found to have herniated through a tear in the peritoneum that was created, but unnoticed, during the hernia repair. The patient underwent successful reoperation with the laparoscopic technique. Testicular pain was more common in the TEP group ($P = .003$), occurred in the early postoperative period, and settled after a period of weeks to months. One year after surgery, all patients had normal testes on clinical examination. Hematomas were more often found in the Lichtenstein group ($P = .03$). Two patients in the open repair group had wound infection develop. These infections consisted of erythema around the wound that resolved with oral antibiotics. The Lichtenstein group showed a higher frequency of impaired sensibility in the inguinal area compared with the TEP group ($P < .0001$). Overall, 46 of 81 patients (57%) in the laparoscopic group and 59 of 87 patients (68%) in the open repair group had any of the complications presented in Table II ($P = .14$).

No recurrences were seen at the 6-week follow-up. However, 2 recurrences were found on clinical examination 1 year after surgery (Table II). Both were primary hernias operated with the TEP technique. In 1 of the 2 patients, the dissection at the TEP operation was reported as troublesome. The 2 recurrences have undergone reoperation with open repair.

One year after surgery, patient satisfaction with the hernia operation was estimated on a visual analogue scale, from 0 (the worst) to 100 (the best). The median value for the TEP group was 100 (range, 18 to 100) and for the open group was 98 (range, 30 to 100; $P = .53$, Mann-Whitney U test).

The mean costs per patient in the TEP group and the open repair group, respectively, are presented in Table IV. The estimated costs in the laparoscopic group included costs of rerepair of the 2 recurrences and the small bowel obstruction. These reoperations added a direct cost of $91 per patient in the laparoscopic group. The direct costs of the TEP operation were $1091 higher than those of the group with Lichtenstein repair ($P < .001$). With inclusion of the indirect costs (ie, cost for sick leave), the TEP technique was not more expensive than the open mesh repair ($P = .21$).

DISCUSSION

Hernia repair is a common surgical procedure. However, until only a few years ago, hernia repair was associated with a high incidence rate of recurrence. Furthermore, a second operation is more troublesome than the initial one. Because many of the patients who undergo operation for hernia are of a working age, the treatment of inguinal hernia not only is of importance for the individual but also has great socioeconomic impact.

Laparoscopic techniques for inguinal hernia were introduced to reduce hernia recurrence and facilitate patient recovery and return to work. Several trials comparing the new techniques with open procedures have been published during recent years.[1-15] Often, however, the control groups have consisted of a variety of open conventional hernia techniques[1-10] and open tension-free mesh techniques.[11-15] A metaanalysis of randomized controlled trials has shown an advantage in postoperative pain for laparoscopic hernia repair compared with opened sutured repair but not compared with open tension-free repairs.[16] Both types of open techniques had a longer recovery time than the laparoscopic technique.[16]

A large systematic review, which did not include studies comparing laparoscopic extraperitoneal techniques (TEP) with Lichtenstein, has confirmed that patients with laparoscopic hernia repair returned to daily activities sooner.[10] Other studies have not been able to show a shortening in sick leave.[4,5] However, the operation time was longer, and furthermore, there appeared to be a higher

Table IV. Mean cost* per patient

	Open repair	*Laparoscopic repair*	*P value*
Theater cost (15.57 US$/min)	1480	2084†	<0.001
Disposables	46	512†	<0.001
Hospital stay	200	221†	0.20
Summary of direct costs	1726	2817†	<0.001
Total cost (indirect included)	4408	4757†	0.21

*Values are in US$. US$ 1 = SEK 8.09, 31 Dec 1998.
†The estimated costs of reoperation for the small bowel obstruction and for the two recurrent hernias are included.

rate of serious complications, including visceral and vascular injuries, with the laparoscopic approach.[10] The potentially serious intraoperative complications all followed the TAPP inguinal hernia repair.

For reduction of the risk for serious intraabdominal complications, a TEP that leaves the peritoneum intact has been introduced.[17-21] In this study, we therefore compared 2 tension-free mesh procedures (ie, the TEP technique) with the Lichtenstein procedure. The latter procedure was introduced to reduce hernia recurrence and, indeed, has shown reproducibly low recurrence rates.[22,23]

In this study, patients who underwent operation with the TEP technique consumed less analgesic after surgery and had a shorter time to complete recovery and return to work. From a principle point of view, the main differences between the TEP and Lichtenstein techniques are the size of the wound and the way the mesh is fixed to the abdominal wall. Thus, one could speculate that the short-term advantages that we found in favor for the TEP technique are mainly related to a smaller amount of traumatized tissue.

The previous 2 randomized studies that compared TEP repair and Lichtenstein repair also showed advantages for the endoscopic operation in terms of postoperative pain,[24] hospital stay,[24] and return to normal life and work.[25] However, 1 of the 2 studies had a short follow-up time (1 week), and no attempt to evaluate recurrence rates was seen.[24] The other study was based on only 45 randomized patients with a median follow-up period of 10 months.[25]

No difference was seen in overall complications between the 2 groups. However, patients in the Lichtenstein group had a higher frequency of clinically observed postoperative hematomas. This observation must be interpreted with some caution because possibly the same amount of blood that gives rise to a clinically observed hematoma in the Lichtenstein repair sometimes may be hidden in the preperitoneal space and never rise to the surface in the case of a TEP repair. Fewer hematomas in the laparoscopic hernia repairs compared with various open repairs have previously been reported.[10] A higher incidence rate of testicular pain in the early postoperative period was noted in the TEP group. The reason for this condition is unknown, but it may be related to trauma to the cord structures with dissection of the sac from the cord. However, the pain settled after a period of weeks to months; 1 year after surgery, all patients had normal testes on clinical examination. Wright and coworkers[24] have also described transient testicular pain after TEP. Of greater concern, 1 patient in the laparoscopic group underwent reoperation on the third postoperative day for small bowel obstruction. This complication was from an unnoticed peritoneal rift during the primary operation, and hence, technique-specific.

The laparoscopic approach to hernia repair reduces the likelihood of nerve injury to the ilioinguinal and iliohypogastric nerves but not nerve injuries to the nervus lateral cutaneus and the femoral part of nervus genitofemoralis.[26] In agreement, in this study, a higher frequency of impaired sensibility in the inguinal area was found in the Lichtenstein group compared with the TEP group at the follow-up. However, no difference was seen in reported neuralgia.

The learning curve for TEP is increased compared with both conventional hernia surgery[21] and TAPP.[18] Therefore, TEP has been suggested to be undertaken only by experienced laparoscopic surgeons—for instance, surgeons who have performed more than 100 laparoscopic cholecystectomies.[21] In our study, all 3 surgeons also had performed about 100 laparoscopic cholecystectomies each before they started to perform TEP. However, the definition of an experienced laparoscopic surgeon is still a matter of opinion rather than a matter of fact. This study did not address this issue, and no attempt was made to evaluate the learning curve.

The thought that laparoscopic hernia repair may be more attractive in specific types of her-

nias, such as bilateral and recurrent hernias, is reasonable. In recurrent hernia, the laparoscopic approach avoids the previously operated field, which theoretically should decrease the complication rate.[27] In bilateral hernia, the operation can be performed through the same incisions, which potentially could decrease postoperative morbidity.[14,27,28] This study included patients with primary and recurrent hernias and bilateral hernias. However, the number of patients with these 2 conditions was too small to allow a scientific evaluation. We therefore think that future randomized studies should preferably be concentrated on these subgroups. Given the decreased incidence rate of surgery for recurrent inguinal hernia, such studies inevitably have to be made on a multicenter basis.

On the basis of our results, we hypothesize that not just 1 hernia repair technique should be recognized as the golden standard for all patients. More likely, the operation technique, for best result and cost effectiveness, must be individualized. In general, the laparoscopic technique is more expensive concerning hospital costs (direct costs),[2,5,6] which was confirmed in this study. Development of reusable instead of disposable instruments for laparoscopic hernia repair can reduce this difference. In our study, about half the excess in direct cost for the TEP group compared with the open group was from disposables, and the other half was from a longer operation time. However, the indirect cost (from sick leave) can counterbalance the difference between the 2 groups or even make the laparoscopic more cost-effective.[2,13,15] In this study, no statistically significant difference was seen in the total costs between the TEP group and the open group.

In our study, 2 recurrences were found in 97% of included patients who underwent examination 1 year after surgery. Both were in the laparoscopic group. Most hernia recurrences occur within 5 years of the procedure, but it is well-known that recurrences can show up much later.[29] At present, there is no long-term follow-up after laparoscopic hernia repair. Therefore, the long-term rate of recurrence cannot be estimated.

In conclusion, patients who underwent operation with the TEP technique consumed less analgesic after surgery and returned to work earlier than patients who underwent operation according to Lichtenstein. However, the TEP technique was associated with a higher direct cost. No difference was seen in overall complications, although 1 technique-specific complication was found in the TEP group. Future randomized studies should therefore focus on subgroups of patients who could potentially benefit from a laparoscopic approach.

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Paper II

Original Communications

Laparoscopic extraperitoneal inguinal hernia repair versus open mesh repair: long-term follow-up of a randomized controlled trial

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Background. *We have conducted a randomized controlled trial of totally extraperitoneal hernia repair (TEP) versus tension-free open repair (Lichtenstein repair); we have presented the results previously up to 1 year after the operation. The aim of this study was to compare patient outcome in both groups at a median follow-up of 7.3 years after operation.*
Methods. *Of 168 patients included in a prospective, randomized controlled trial designed to compare TEP with an open tension-free technique, 154 patients (92%) answered a questionnaire and 147 patients (88%) were followed up at an outpatient clinic after a minimum of 6 years after operation.*
Results. *Overall, 89% of patients in the TEP group and 95% of patients in the open group reported complete long-term recovery (*P *= .23). Permanent impaired inguinal sensibility was more common in the open group (*P *= .004), whereas the proportion of patients with reported testicular pain was higher in the TEP group (*P *= .003). Three recurrences were found in the TEP group, and 4 recurrences were found in the open group (*P *= .99). Four patients in the TEP group underwent operations for complications related to the hernia repair (small bowel obstruction, umbilical hernia, testicular pain, and neuralgia).*
Conclusion. *Overall, both groups showed good long-term results with low rates of recurrences. However, the TEP group was associated with a higher proportion of patients with long-term testicular pain, whereas impaired inguinal sensibility was more common in the open group. (Surgery 2008;143:313-7.)*

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THE DRAMATICALLY DECREASED incidence of hernia recurrences that has been demonstrated in recent years has been shown to be associated with the use of mesh rather than with the method used to place the mesh.[1] Therefore, hernia repair using mesh, especially open tension-free techniques, has become the method of choice for most surgeons.[2,3] With a low recurrence rate, other long-term complications have been more important clinically; concerns have been raised about the long-term safety of implantation of mesh material and the risk of chronic pain after modern hernia repair.[4,5]

Several randomized controlled studies and reviews confirm that laparoscopic techniques with tension-free mesh are associated with short-term advantages such as less postoperative pain, a shorter time to full recovery, and an earlier return to work compared with open techniques.[1,6-8] So far, randomized studies that present long-term results are scarce.[9,10] However, recent studies have suggested that laparoscopic mesh placement is associated to a lesser degree with chronic pain than open procedures.[5]

We have conducted a randomized controlled trial of TEP versus tension-free open repair, and we have presented previously the results up to 1 year after the operation.[6] The aim of this study was to compare long-term outcome in the TEP group and in the open repair group.

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PATIENTS AND METHODS

A detailed description of inclusion/exclusion criteria, intervention, evaluation, and sample size has been reported previously.[6]

Study population. Between 1996 and 1997, as described previously, 168 patients aged 30 to 65 years were enrolled in a prospective, randomized trial that compared a laparoscopic tension-free repair (TEP technique) and an open tension-free technique (Lichtenstein technique).[6] The trial was conducted at Lund University Hospital, Lund, Sweden. The results up to 1 year after the operation have been presented before.[6] Eighty-one patients were randomized to TEP, and 87 patients were randomized to open repair.

Evaluation. A flowchart that summarizes the study is shown in the Fig. After approval from the Ethical Committee of the Medical Faculty of Lund University, all participants were mailed a reply-paid comprehensive questionnaire at a minimum of 6 years after the operation. The questionnaire included questions regarding pain in the groin or testicle, impaired sensibility (defined as loss of the ability to register touch, an unpleasant sensation produced by normal touch, or the presence of numbness and tingling), complete recovery, impact of the operation on day-to-day life, and whether the patient was satisfied with the results of the operation and recovery. Questions were also included about the presence of a recurrent lump in the treated groin, operation for recurrent hernia, and development of a lump in the nontreated groin.

All patients who returned the questionnaire and provided their written informed consent were contacted subsequently by telephone for complementary questions and information. They were also offered a follow-up consultation at the outpatient clinic by the same independent surgeon (M.H.) who performed the 1-year follow-up. At this follow-up, the inguinal area was examined, impaired sensibility was recorded, and atrophy of the testicle was registered. The presence of recurrent hernia, which is based on clinical examination that shows a palpable reducible lump in the treated groin or in clinically uncertain cases with herniography, was recorded. When applicable, the patient was asked to provide a more thorough pain history.

Statistics. Analysis of outcome measures for the TEP group and the open group was performed on an intention-to-treat basis. The results for continuous variables are presented as median (range) if not stated otherwise. For categorical data, absolute numbers in addition to percentages are provided. For numeric data, differences between groups were analyzed with the Mann–Whitney *U* test. The χ^2 test was used for categorical data, except when expected frequencies were less than 5, when the Fisher exact test was used. A probability level of a random difference of *P* less than .05 was considered significant.

RESULTS

The study included 140 patients with primary hernia (including 10 bilateral cases) and 28 patients with recurrent hernia.[6] Of 168 patients included in the prospective, randomized controlled trial, 165 patients (98%) were alive after a minimum of 6 years after operation. In all, 154 patients (92%) answered the questionnaire, and 147 patients (88%) were followed up at the outpatient clinic (Fig). Median follow-up was 7.3 years (range, 6.1–8.9 years).

Overall, 89% of patients in the TEP group and 95% of patients in the open group reported complete long-term recovery ($P = .23$). In the questionnaire, patients were asked to estimate the operation's impact on their day-to-day living on a visual analog scale, from 0 (no impact) to 100 (total impact). The median value for the TEP group was 4 (range, 0 to 86), and the median for the open group was 5 (range, 0 to 69) ($P = .15$).

Through the questionnaire and the clinical examination, long-term complications were recorded and they are listed in the Table. As can be observed, permanent impaired inguinal sensibility was more common in the open group, whereas the proportion of patients with reported testicular pain was higher in the TEP group. Severe pain was only observed in 6 patients (4 patients in the TEP group and 2 patients in the open group). However, only 1 patient reported a regular need of analgesic and long-term sick leave. Four patients in the TEP group and 5 patients in the open group reported that the operation had a long-lasting negative impact on their ability to move ($P = .99$).

As reported previously,[6] 2 recurrences were found 1 year after operation, both in the TEP group. At the long-term follow-up, 1 additional recurrence in the TEP group and 4 recurrences in the open group were noted. In 6 of 7 recurrences, the diagnoses were based on clinical examination that showed a palpable lump in the treated groin. In the remaining patient, the clinical examination was uncertain, and a herniography confirmed the recurrence. Interestingly, in the questionnaire, the reported number of recurrences was 8. However, in 1 patient, clinical examination and herniography ruled out a recurrent hernia.

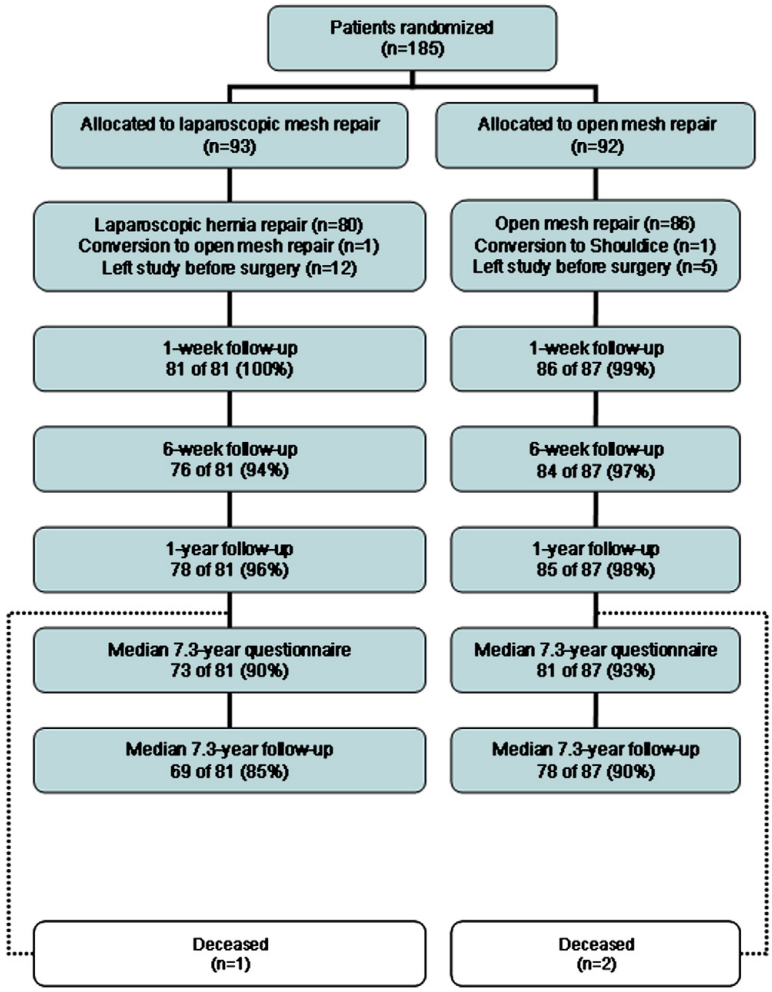

Figure. Flowchart that summarizes this prospective controlled trial comparing TEP and tension-free open repair (Lichtenstein repair).

Fifteen patients in the TEP group and 13 patients in the open group developed a new primary hernia in the contralateral groin ($P = .47$).

At follow-up, 4 patients, who were all in the TEP group, have been operated for conditions related to the hernia repair. As reported previously,[6] 1 patient underwent laparoscopic reoperation 3 days after the primary operation for small bowel obstruction. One patient suffered from severe chronic testicular pain caused by impaired testicular circulation, and an orchiectomy was performed. Still another patient developed an umbilical hernia that was repaired surgically. Finally, 1 patient with severe inguinal neuralgia underwent a surgical exploration with neurolysis after long-term conservative treatment.

DISCUSSION

This prospective, randomized controlled study compared the long-term results, median 7.3 years after operation, of a laparoscopic TEP with the results of an open tension free technique (Lichtenstein repair). We have published previously data up to 1 year after operation.[6]

Table. Long-term complications and recurrences

	TEP n = 73	*Open mesh repair n = 81*	P *value*
Impaired inguinal sensibility yes/no	9/73	26/81	.004
Groin pain yes/no	6/73	11/81	.32
Testicular pain yes/no	10/73	1/81	.003
Testicular atrophy yes/no	2/69	3/75	.99
Umbilical hernia yes/no	1/69	0/78	.99
Neuralgia yes/no	1/69	0/78	.99
Hydrocele yes/no	1/69	0/78	.99
Recurrence yes/no	3*/69	4/78	.37
Contralateral hernia yes/no	15/73	13/81	.47

*2 of 3 recurrences were diagnosed at the 1-year follow-up.

This study differs from other randomized studies[9,10] because it presents long-term follow-up data for 2 well-defined operative methods, and it is to our knowledge the first randomized study that presents long-term data on TEP versus Lichtenstein.

Overall, both the TEP group and the open group were associated with good long-term results with high reported rates of complete recovery and low numbers of recurrences. The latter is well in agreement with previously published results that have shown a dramatic reduction in the incidence of hernia recurrences after the introduction of mesh repair per se.[1]

With a low recurrence rate, other long-term complications have been more important clinically, and concerns have been raised about the long-term safety of implantation of mesh material and the risk of chronic pain after modern hernia repair.[4,5] In the current study, all recorded long-term variables, except for testicular pain and impaired sensibility, showed no differences between the TEP group and the open repair group.

However, chronic testicular pain was more common in the TEP group. For 1 patient with impaired testicular circulation, an orchiectomy to relieve the pain was performed. In general, the reason why this condition is more common after TEP is unknown, but it may be related to trauma to the cord structures, which include the genital branches of the genitofemoral nerve, with the dissection of the sac from the cord. Wright et al[9] have also reported that patients who underwent TEP repair were more likely to have long-term testicular pain, whereas the UK Medical Research Council Laparoscopic Groin Hernia Trial found no difference in the rate of testicular pain.[10]

In contrast to testicular pain, permanent impaired inguinal sensibility was more common in the open group compared with the TEP group. This phenomenon is explained most probably by the fact that the laparoscopic approach decreases the likelihood of nerve injury to the ilioinguinal and iliohypogastric nerves. Others have reported the same results.[10]

Of greater concern was that, except for the hernia recurrences, 4 patients in the TEP group underwent operations for complications related to the hernia repair (small bowel obstruction, umbilical hernia, testicular pain, and neuralgia). All these complications were distributed evenly over the whole period of the study and were not only associated with the start of the study. Concerns have been raised previously concerning serious complications after laparoscopic hernia repair, although they have been described after using the transabdominal technique.[1,11] However, the above-presented complications in the TEP group, although not that serious, are in the negative balance for the technique.

A possible weakness of the study, in terms of interpreting the results, was that it included both primary and recurrent hernias. However, given the small number of recurrent hernias, this inclusion probably has only slightly clouded the data. The number of recurrences included was also too small to allow subgroup analyses.

Some major benefits of the current study are a high long-term follow-up rate of about 90% and that it is based on both questionnaire and a direct physician contact. The latter was carried out by a surgeon (M.H.) who had not participated in the patient's operation. The same surgeon performed the follow-up 1 year after operation. We have a clear impression that the direct physician contact beyond statistics have strengthened our results not the least by helping us to grade severity of symptoms otherwise missed by the questionnaire. Most other comparable studies are based on questionnaires.

Taken the current data and our previously presented results[6] together, our data support the concept of individualizing hernia repair for the best results and cost effectiveness. For instance, TEP is an excellent method for individuals in a working population with primary hernias (1-sided or bilateral) who require a short convalescence. It also has advantages in recurrent hernias because it avoids the previously operated field.[12] In this context, however, it is also important to take into account the experience of the center and the surgeon for a specific technique.

In conclusion, with a minimum follow-up of 6 years, long-term cure of hernia in patients operated with TEP and Lichtenstein techniques was excellent. However, the higher proportion of patients with chronic testicular pain in the TEP group remains a cause of concern.

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Paper III

Male infertility after mesh hernia repair: A prospective study

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Background. *Several animal studies have raised concern about the risk for obstructive azoospermia owing to vasal fibrosis caused by the use of alloplastic mesh prosthesis in inguinal hernia repair. The aim of this study was to determine the prevalence of male infertility after bilateral mesh repair.*
Methods. *In a prospective study, a questionnaire inquiring about involuntary childlessness, investigation for infertility and number of children was sent by mail to a group of 376 men aged 18–55 years, who had undergone bilateral mesh repair, identified in the Swedish Hernia Register (SHR). Questionnaires were also sent to 2 control groups, 1 consisting of 186 men from the SHR who had undergone bilateral repair without mesh, and 1 consisting of 383 men identified in the general population. The control group from the SHR was matched 2:1 for age and years elapsed since operation. The control group from the general population was matched 1:1 for age and marital status.*
Results. *The overall response rate was 525 of 945 (56%). Method of approach (anterior or posterior), type of mesh, and testicular status at the time of the repair had no significant impact on the answers to the questions. Nor did subgroup analysis of the men ≤40 years old reveal any significant differences.*
Conclusion. *The results of this prospective study in men do not support the hypothesis that bilateral inguinal hernia repair with alloplastic mesh prosthesis causes male infertility at a significantly greater rate than those operated without mesh. (Surgery 2011;149:179-84.)*

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GROIN HERNIA REPAIR IN MEN is among the most common operative procedures in the world. Over the past 20 years, the use of mesh bioprosthesis in hernia repair has increased rapidly. Currently the open and laparoscopic, mesh-based, tension-free operative methods dominate. Among the advantages of mesh repair are the low recurrence rate, short learning curve, and rapid return to physical activity. The use of alloplastic mesh prosthesis in inguinal hernia repair is thus cost effective for the patient as well as for the health care and social insurance systems.

It is well known that alloplastic mesh causes an inflammatory response and a foreign body reaction in adjacent tissues. The resulting fibrosis of the inguinal wall is suggested to be 1 of the reasons for the low recurrence rate. Whether or not the mesh is applied from an anterior approach, for example, according to the Lichtenstein technique,[1] or from a posterior approach, as in laparoscopic repair, the mesh is placed in direct contact with the spermatic cord. Several animal studies in various species have reported that the structures of the spermatic cord also react to the mesh,[2-6] especially the edge of the mesh.[3] Thickening of the wall of the vas deferens with narrowing and obstruction of the lumen at the site of the mesh but not proximal to it have been observed and discussed.[3] In contrast, others have found proximal dilatation but no thickening of the wall of the vas deferens.[2] Decreased arterial perfusion in the testis[5,7] and spermatic venous thrombosis[4] have also been reported. One study has shown beneficial effects on the integrity of the vas deferens when using lightweight mesh,[3] whereas another study did not find any difference

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in inflammation and fibrosis when comparing heavyweight with lightweight mesh.[8]

Over the past 10 years, a few reports suggested that the use of mesh for male inguinal hernia repair could cause male infertility, most often by obstructive azoospermia.[9,10] Men operated with bilateral mesh hernia repair or men with unilateral repair and impairment of the contralateral testis have been considered to be at the greatest risk. Some authors even suggest that the risk for infertility after mesh repair is of such importance that surgeons should not generally recommend this technique for young men. Because most of these reports are based on a limited number of cases,[9,10] their conclusions have been questioned and some consider the studies inadequate and not valid enough for more explicit conclusions.[11] In contrast, the avoidance of hernia recurrence is still considered to be of major importance.[12] The discussion has been further complicated by the notion that operation for inguinal hernia may instead improve male fertility. There has also been discussion whether or not the proposed risk is of such importance that some or all patients undergoing hernia surgery should be informed in detail preoperatively, even if this may cause some to choose a method associated with greater risk for recurrence and long-term pain.[10,11] Recommendations have also been made to leave the cremaster muscle intact as a protective layer[4] and to dissect the spermatic cord carefully and meticulously, to avoid damaging its structures.[13] A technique for reestablishing patency in the vas deferens has also been described.[14]

Most authors agree that we are still not sure whether the risk for postoperative infertility is relevant, and more human studies have been requested.[3,11,15] The frequency and clinical relevance of azoospermia after mesh hernia repair has, to our knowledge, not been evaluated in any large, prospective study. The purpose of this study was to determine the prevalence of infertility, measured as involuntary childlessness, in men who hypothetically may run a high risk for azoospermia, namely, those of a fertile age who have undergone bilateral mesh hernia repair.

METHODS

The present study is based on data from the Swedish Hernia Register (SHR), which collects many different data, including method of repair, type of mesh used, and testicular status at the time of the hernia repair. The register (available from: www.incanet.se/Svenskt-Brackregister) covers almost 100% of hernia repairs performed in Sweden and at present >180,000 repairs have been recorded. Because every Swedish citizen can be traced by their unique personal registration number, any further repair on the same patient, performed in Sweden, can be traced and cross-checked with the National Population Register.

Two groups were assembled from the SHR, 1 consisting of patients operated bilaterally with mesh and 1 of men operated bilaterally without mesh. The groups were matched for age and time elapsed since last repair. Because bilateral repairs without mesh were much less common than repairs with mesh, thereby limiting the size of the study, this group was identified first. The mesh group was then matched to the nonmesh group 2 cases to 1. Included were men aged 18–55 years. Men who had undergone >1 repair on the same side were excluded. A second control group, matched for age and marital status, was assembled from the National Population Register. This control group consisted of 1 subject for each man operated bilaterally with mesh.

In April 2009, all men in the 3 groups received the same questionnaire by mail. The questionnaire included the questions listed in Table I. There was also an additional question inquiring about previous hernia repair addressed to the controls assembled from the general population. Three weeks after the questionnaire was distributed a reminder was sent to nonresponders.

The difference in numbers of children born after the last repair was tested with the Student *t* test. For all other questions, the differences between the groups were tested with Chi-square test. $P < .05$ was considered significant. The results for continuous variables are presented as mean values ± standard deviation (SD) if not stated otherwise. For categorical data, absolute numbers in addition to percentages are provided. All 3 groups were included in comparisons regarding the first 2 questions (involuntary childlessness and investigations for infertility the last 5 years). The remaining questions were not applicable for the control group from the general population.

RESULTS

Altogether, 192 men aged 18–55 years operated bilaterally without mesh were identified in the SHR. These men were matched 1:2 with 384 men operated bilaterally with mesh and 1:2 with 384 men from the general population. There were 8 men in the bilateral mesh repair group, 6 men in the nonmesh bilateral repair group, and 1 in the general population group who had

Table I. Outcome of the questionnaire

	Operated bilaterally with mesh		*Operated bilaterally without mesh*		*Controls from the general population*	
	Positive responses/ total number of responders	*% (95% confidence interval)*	*Positive responses/ total number of responders*	*% (95% confidence interval)*	*Positive responses/ total number of responders*	*% (95% confidence interval)*
1. Have you had a period of ≥1 of involuntary childlessness during the last 5 years?	15/232	6.5 (3.3–9.6)	10/111	9.0 (3.7–14.3)	14/201	7.0 (3.4–10.5)
2. Have you undergone investigation for infertility the last 5 years?	6/229	2.6 (0.6–4.7)	5/112	4.5 (0.6–8.3)	9/201	4.5 (1.6–7.3)
3. Did you have any children before the hernia repair?	120/228	52.6 (46.2–59.1)	61/111	55.0 (45.7–64.2)	Not applicable	
4. Did you have a period of ≥1 year of involuntary childlessness before the hernia repair?	14/229	6.1 (3.0–9.2)	6/110	5.5 (1.2–9.7)	Not applicable	
5. Have you made any attempts to have children after the hernia repair?	58/230	25.2 (19.6–30.8)	31/112	27.7 (19.4–36.0)	Not applicable	
6. Have you had a period of ≥1 year of involuntary childlessness after the hernia repair?	14/89	15.7 (8.2–23.3)	11/48	22.9 (11.0–34.8)	Not applicable	
7. Have you undergone investigation for infertility after the hernia repair?	3/89	3.4 (0.0–7.1)	4/48	8.3 (0.5–16.2)	Not applicable	
	Total number of responders	Mean number of children ± standard deviation	Total number of responders	Mean number of children ± standard deviation		
8. How many children have you had after the last hernia repair?	91	0.9 ± 0.9	46	0.8 ± 0.7	Not applicable	

emigrated or died at the time the questionnaire was administrated.

The response rates were 232 of 376 (62%) in the bilateral mesh repair group, 112 of 186 (60%) in the bilateral nonmesh repair group, and 181 of 383 (53%) in the control group. All data presented are based on the responders. Responders and nonresponders did not differ in age and marital status (Table II). The mean age was 42.3 ± 8.8 years in the bilateral mesh repair group, 43.4 ± 8.8 years in the bilateral suture repair group, 43.1 ± 8.1 years in the control group. Altogether 179 (33%) were

Table II. Marital status

	Operated bilaterally with mesh, n *(%)*	*Operated bilaterally without mesh,* n *(%)*	*Controls from the general population,* n *(%)*
Married	107 (46.1)	50 (44.6)	95 (47.0)
Unmarried	95 (40.9)	47 (42.0)	93 (46.0)
Divorced	30 (12.9)	15 (13.4)	14 (6.0)
Total	232 (100)	112 (100)	202 (100)

≤40 years of age when they answered the questionnaire. There was no significant difference in age between the 2 hernia repair groups and the control group. Mean time elapsed since the last repair in the 2 groups from the SHR was 6.9 ± 3.3 years. There was no significant difference in time elapsed since the last repair between the 2 groups. Testicular atrophy or absence of the testicle on the side operated was noted in 6 (1.1%) of the repairs. Lightweight meshes were used in 17 patients (4.9%) with mesh repairs. The mesh repairs were performed via an anterior approach in 435 (80%) patients and via a posterior, open, or laparoscopic approach in 111 (20%) patients. There were 16 (8%) subjects in the control group assembled from the general population who stated that they had undergone hernia repair.

There were no differences between the groups for any of the questions, including questions inquiring about involuntary childlessness, infertility investigation, and number of children (Table I). Subgroup analysis of men ≤40 years did not reveal any significant differences. Method of approach (anterior or posterior), type of mesh, and testicular status at the time of the repair had no significant impact on the answers to the questionnaire.

DISCUSSION

The results of this prospective study in men do not support the hypothesis that inguinal hernia repair with mesh causes male infertility at a significantly greater rate than those operated without mesh. The men included in the analysis, that is, young men who had undergone repair on both sides using alloplastic mesh prosthesis, represent a group that hypothetically runs the greatest risk of infertility if the use of mesh has a substantial impact on the risk for obstructive azoospermia. Because no increase in risk was seen after bilateral mesh repair, unilateral use of mesh should be even safer as far as infertility is concerned. The findings were also confirmed by the results of a subgroup analysis of the youngest men in our study.

This study was not designed to determine whether bilateral hernia surgery in males increases the risk for infertility per se, but rather to explore the effect of the mesh. Our results do not indicate that there is a substantial risk with those methods included in our study.

Infertility is a serious complication, especially in young men who may later wish to conceive a child. It cannot be ruled out that the relatively high rate of nonresponders obscures a risk increase not detected in the study. Nevertheless, these results do not indicate that the risk of infertility is of such magnitude that the mesh technique should be avoided in young men. The advantages of the mesh method seems to outweigh potential drawbacks, at least outside centers specialized in nonmesh inguinal hernia repair with comparable recurrence rates. Increasing the use of nonmesh methods would most likely lead to an unwanted increase in recurrences and more reoperations, because the introduction of mesh repairs has decreased the rate of recurrences.[12] Reoperation may be even more traumatic to the spermatic cord than any primary repair, whether it is performed with or without mesh.

The more radical dissection along the spermatic cord and resection of cremaster muscles required to perform a sutured repair may, in fact, be more harmful than the mesh itself. It may be argued that the trauma and ischemia to the vas caused by the more extensive dissection is associated with a greater risk for injury to the vas deferens than the fibrosis caused by the mesh. Our study, however, did not provide any statistical evidence for this hypothesis.

In mesh operations, the recommendation of using the intact cremasteric muscle as a protective layer for the spermatic cord structures is theoretically preferable and recommended by some.[4] This maneuver is possible only when the mesh is placed over the posterior wall. Regarding infertility, our study found no differences between the mesh methods, but the study design was not designed to answer that question; we do not know how the spermatic cord and the cremasteric muscle were treated in each Lichtenstein operation. Moreover, the Lichtenstein group is numerically dominating in our material.

In the control group from the general population, 7% stated that they had experienced a period of 1 year of involuntary childlessness (Table I). The sample size of the study responders was sufficient to achieve a statistical power of 80% to detect a hypothetical doubled risk in the mesh repair group at the $P < .05$ level. Considering the fact that the men in the bilateral mesh group actually gave fewer positive responses than the control groups to most of the questions, the statistical power is even greater. The risk of these findings being the result of a type II error is, thus, relatively small, at least if a risk increase greater than a factor of 2 is assumed.

Our study does have some limitations. Not unexpectedly, and probably because many of the questions concerned matters that may be perceived as quite intimate, the response rate was relatively low, despite the reminder. Although it cannot be excluded that the prevalence of infertility may have differed between responders and nonresponders, the groups did not differ in terms of age or marital status. Although the willingness to answer the questionnaire may be affected by a history of involuntary childlessness, there is no obvious reason to believe that it could be affected by the method of hernia repair. The risk of a systematic selection bias decreasing the difference between the mesh group and nonmesh group is small, although the overall prevalence of infertility may have been affected by selection of responders.

We are well aware that the etiologies of involuntary childlessness are multiple and involve both partners; however, the power of the study was sufficient to detect a hypothetical influence from the use of mesh despite a high background prevalence of involuntary childlessness. Analyses of the spermiogram would, of course, have been an even more reliable method to diagnose male infertility, but when designing the study, we expected that patients would find that method to be too intimate and thereby give us a very low response rate, making the results useless.

The risk for infertility after mesh repair, as proposed by other authors,[4,5,9,10] has been regarded as an important question. Our results indicate that at the informed consent, the surgeon should not focus on the infertility problem. To advise a man to undergo a hernia repair with a mesh method must be regarded as a recommendation based on the most recent clinical evidence.

In our opinion, cryopreservation of sperm before hernia operations in young men, with or without mesh, is not necessary. It may be indicated in selected cases before bilateral inguinal hernia operations and when performing unilateral operations in men with a medical history and clinical findings indicative of testicular dysfunction or abnormalities of the vas deferens on the contralateral side. This concept includes testicular atrophy and a history of previous operations that could have harmed the testicle or the vas deferens. Local legal circumstances and health care policies may also have to be taken into consideration when deciding on cryopreservation of sperm. Finally, the decision must be taken by the patient together with the surgeon responsible. Cost effectiveness will also be taken into account in those countries where the national health care system covers the cost and in those countries where economic resources are very limited.

In conclusion, the study showed no increase in involuntary childlessness in men who had undergone bilateral mesh repair. Although it cannot be ruled out that there may be a minor increase in risk not detected in this study, it is very unlikely that this increase would be great enough to outweigh all advantages of mesh repairs in comparison with sutured repairs. In our opinion based on the results of this study, mesh repair could continue to be the method of choice in hernia surgery.

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Paper IV

Mesh hernia repair and male infertility: A retrospective register study

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Background. *Previous studies have suggested that the use of mesh in groin hernia repair may be associated with an increased risk for male infertility as a result of inflammatory obliteration of structures in the spermatic cord. In a recent study, we could not find an increased incidence of involuntary childlessness. The aim of this study was to evaluate this issue further.*
Methods. *Men born between 1950 and 1989, with a hernia repair registered in the Swedish Hernia Register between 1992 and 2007 were cross-linked with all men in the same age group with the diagnosis of male infertility according to the Swedish National Patient Register. The cumulative and expected incidences of infertility were analyzed. Separate multivariate logistic analyses, adjusted for age and years elapsed since the first repair, were performed for men with unilateral and bilateral repair, respectively.*
Results. *Overall, 34,267 men were identified with a history of at least 1 inguinal hernia repair. A total of 233 (0.7%) of these had been given the diagnosis of male infertility after their first operation. We did not find any differences between expected and observed cumulative incidences of infertility in men operated with hernia repair. Men with bilateral hernia repair had a slightly increased risk for infertility when mesh was used on either side. However, the cumulative incidence was less than 1%.*
Conclusion. *Inguinal hernia repair with mesh is not associated with an increased incidence of, or clinically important risk for, male infertility. (Surgery 2012;151:94-8.)*

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Inguinal hernia is one of the most common conditions requiring surgical treatment. Hernia repair techniques have varied over the years. The last 2 decades have witnessed the use of alloplastic mesh-based, tension-free methods gradually replacing traditional sutured techniques. Most surgeons regard mesh repair as the method of choice whether performed laparoscopically or by open technique. The low recurrence rate, short learning curve, and rapid return to physical activity make it cost-effective and safe in the short as well as in the long run.[1] This is of importance not only for the patient but also for the social insurance system. The alloplastic mesh causes an inflammatory response and a foreign-body reaction in the adjacent tissues, and the resulting fibrosis of the inguinal wall is suggested to be the main reason for the stability of the repair and the low recurrence rate.

The complications of hernia surgery are much more common and severe in patients undergoing repair in a previously operated groin.[2] In most studies comparing different methods for groin hernia repair, the long-term recurrence rate is considered to be the most important single study outcome variable. So far, little attention has been paid to method-specific complications. Mesh techniques, however, have reduced recurrence rates to such low levels that other aspects have now become more important as outcome measures, including chronic pain[3,4] and infertility.

A growing number of reports from animal studies have voiced the possibility that the use of mesh in male hernia repair may cause infertility as

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a result of obliteration of the vas deference (obstructive azoospermia) or obliteration of the blood vessels in the spermatic cord.[5-8] The results are inconsistent, even though most studies find inflammatory reactions to some extent in the funicular structures. Until now, there have been only a few human studies and case reports on this subject, which together include only a limited number of patients.[9,10] The conclusions and recommendations regarding hernia repair vary in these studies. Some authors do not favor the use of mesh, at least in young men,[5,8] whereas others are still unsure whether this really is an important clinical problem[11] and often emphasize the need for more human studies. Finally, a modified mesh method has been proposed to be safer regarding the so-called infertility problem.[12]

In a recent prospective human register study, we could not find any significant increase in the prevalence of involuntary childlessness after bilateral groin hernia repair with mesh, compared with nonmesh techniques and with the general age-matched male population. To our knowledge, this study is the largest study on this topic so far.[13]

The purpose of this study was to evaluate further the risk for male infertility after groin hernia mesh repair, using a different approach (ie, a retrospective study design in a large population-based cohort).

MATERIALS AND METHODS

All men born between 1950 and 1989 who were registered with a hernia repair in the Swedish Hernia Register (SHR) between 1992 and 2007 were included in the study. Men with both hernia repair and the diagnosis infertility were identified by cross-linking the SHR with the Swedish National Patient Register[14] by searching for the diagnosis "male infertility" (ICD code N46.9). It was not possible to obtain the ICD subcodes (5th position) for the etiology of infertility from the Swedish National Patient Register.

Cumulative incidence of infertility in men operated for groin hernia versus the general population. The observed cumulative incidence of infertility, estimated from the year after the first hernia repair, was compared with the expected cumulative incidence (ie, the calculated incidence that would be expected if it was identical to the general age-matched Swedish male population).

The expected cumulative incidence was estimated by adding together the incidences of newly diagnosed infertility in the total Swedish male population each year after the hernia repair. The incidence of infertility each year was determined by the ratio between the number of men with the diagnosis of infertility and the total number of men born within the same 5-year stratum in Sweden. The total relevant population of Sweden was obtained from Statistics Sweden.[15] For men who had undergone more than 1 repair, the incidence was determined from the year after the first repair.

In the analyses, the men with at least 1 hernia repair were divided into 5 groups depending on the repair:

I. Unilateral repair without mesh
II. Unilateral repair with mesh
III. Bilateral repair without mesh
IV. Bilateral repair with mesh on 1 side
V. Bilateral repair with mesh on both sides

Men who had undergone more than 1 repair on either side were included in a separate group because this constitutes a more heterogenic group and surgical trauma to the vas deferens may have been more extensive. No distinction was made between bilateral repair in 1 synchronous procedure and bilateral repairs on 2 separate occasions.

Mesh versus nonmesh repair and risk for infertility. Two separate multivariate logistic analyses with infertility as the dependent variable were performed: 1 for men who had undergone bilateral repair and 1 for men who had undergone unilateral repair. In both analyses, adjustments were made for age (men born 1965 or later versus men born before 1965) and years elapsed since the first repair. In the analysis of men who had been bilaterally repaired, the laterality was treated as a 3-stage ordinal scale (no mesh, mesh on 1 side, and mesh on both sides).

RESULTS

Altogether 42,775 repairs between 1992 and 2007 in 34,267 men born between 1950 and 1989 were identified in the Swedish Hernia Register (SHR) (Table). A total of 233 of these men also were identified, according to the Swedish National Patient Register, with a diagnosis of "male infertility" (ICD code N46.9) registered the year after the first hernia repair and any time thereafter (Table).

Cumulative incidence of infertility in men operated for groin hernia versus the general population. Observed and expected cumulative incidences of infertility are presented in the Table. None of the groups had an observed cumulative incidence of infertility greater than the expected cumulative incidence. For most groups, the cumulative incidence was even lower than that of the general population.

Table. Observed and expected cumulative incidences of infertility

Group	*Number of men in the hernia register*	*Number of men found to have infertility after the first registered hernia repair*	*Observed cumulative incidence (%, 95% confidence interval)*	*Expected cumulative incidence (%)*
Operated unilaterally without mesh*	6,281	57	0.91 (0.67–1.14)	1.03
Operated unilaterally with mesh*	22,420	133	0.59 (0.49–0.69)	0.67
Operated bilaterally without mesh*	226	0	0†	1.01
Operated bilaterally, mesh on 1 side*	346	3	0.87 (0–18.40)	1.05
Operated bilaterally, mesh on both sides*	2,293	19	0.83 (0.46–1.20)	0.64
Repeated repairs on any side	2,701	21	0.78 (0.45–1.11)	0.68

*No repeated repair on any side.
†Confidence interval not applicable.
Numbers are based on men born between 1950 and 1989 ($N = 34,267$).

Mesh versus nonmesh repair and risk for infertility. In a multivariate logistic analysis of men operated bilaterally, with infertility as the dependent variable and adjusted for age and year elapsed since the repair, a significant difference was observed between men operated with mesh and men operated with suture repair ($P = .030$) (Fig). There was a higher risk for infertility in men who had undergone mesh repair.

In a corresponding multivariate logistic analysis of men operated unilaterally, mesh repair was not found to be significantly associated with an increased risk for infertility ($P = .082$) (Fig).

Power analysis. Assuming that bilateral mesh repair in fact increases the risk 5-fold for developing infertility (from 0.64% to 3.2%), a population of 1,500 men would be sufficient to achieve a 90% chance of detecting a difference at the $P < .05$ level.

Similarly, assuming that unilateral mesh repair increases the risk from 0.67% to 1.0%, a population of 20,000 men would be sufficient to achieve a 90% chance of detecting a difference at the $P < .05$ level.

The sample sizes in the present study were sufficient to reach these levels (Table).

DISCUSSION

This study indicates that male infertility is not a major clinical problem after mesh hernia repair. Even if the risk for infertility is slightly higher for men who have undergone bilateral mesh repair compared with those who have undergone sutured repairs, the cumulative incidence of infertility in this group of patients is so low that the advantages of the mesh technique in every other aspect outweigh this theoretical disadvantage. Thus, mesh techniques should still be considered the methods of choice for these patients.

The size of this retrospective register study is, by far, the largest published. The Swedish Hernia Register (SHR), which includes more than 90% of all inguinal hernia operations performed in Sweden; the Swedish National Patient Register; and the unique Swedish personal number system, which allows all Swedish citizens to be identified and traced, make this type of study possible in our country. We do not know of any other register or system that can repeat this study with the same number of subjects.

This study was designed to reveal any adverse effect of mesh hernia repair regarding male fertility. The design also made it possible to adjust for confounding factors. Although spermiogram, vasography, and testicular biopsy would theoretically enable one to differentiate between the specific causes of infertility, the aim of the present study was not to identify the specific mechanisms behind any infertility incurred. Instead the diagnosis of male infertility was used as a surrogate for the incidence of obstructive azoospermia. In this respect, it is possible that any difference in the cumulative incidence of infertility between mesh and nonmesh methods is in part the result of a vascular lesion affecting the testis and/or obstructive fibrosis affecting the vas deferens. The cumulative incidence of infertility in all groups was lower than expected. We do not know, however, the true incidence, because the rates are only based on

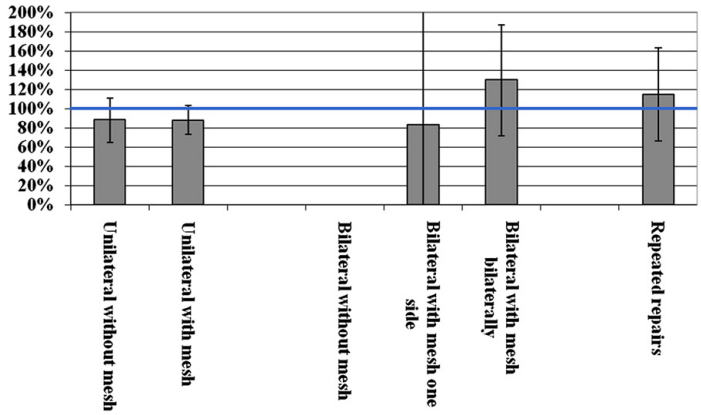

Fig. Observed rates of infertility adjusted for expected rates. The expected risk was estimated by adding the expected risk each year after the first repair determined from the ratio between the total number of men with the diagnosis of infertility each year with the total number of men born within the same 5-year stratum in Sweden. (Color version of figure is available online.)

men seeking health care for infertility. There may have been many more infertile men in the study group as well as in the control population without the desire to have children and, thus, never being found to be infertile. There is no a priori reason to suspect that men in the study group sought health care for infertility in a different manner than men in the control population. Furthermore, most men with the infertility diagnosis were probably part of a couple being evaluated for infertility. There is no reason to believe that these men were given an infertility diagnosis if in fact the female part was the reason for the involuntary childlessness. However, if there existed a small proportion of men who were misclassified, there is no reason to believe that this misclassification would differ between the groups.

The results of this study do not indicate that mesh repair increases the risk for male infertility to the extent that is clinically relevant. The relatively low incidence of infertility resulted in wide confidence intervals for some groups, but a potential increase in any of the groups would be so low that it lacks clinical relevance. The sample size provides sufficient statistical power to detect a hypothetical increase in the risk for infertility of up to 3.2% for men undergoing bilateral mesh repair and 1% for men undergoing unilateral mesh repair. Any undetected increase in risk below these levels is of very little clinical importance. Although men that had undergone bilateral mesh hernia repair had a significantly higher risk for infertility than men who had undergone bilateral repair without mesh on both sides, the incidence is still so low that this increase is to be considered of no clinical importance. The results of this study are thus in accordance with our previous prospective study[13] that showed no increased risk for involuntary childlessness in men that had undergone hernia repair using mesh techniques.

In Sweden, polypropylene is the dominating alloplastic mesh material. Definitive conclusions regarding other mesh material can not be drawn.

The ultimate way of providing definite evidence on the issue of male infertility after mesh hernia repair would be to conduct a prospective randomized clinical controlled study, with detailed examination including semen analysis. Performing such a study would require a very large study sample and long follow-up. Assuming a cumulative incidence similar to that in the present study, a study population of more than 1,000 men would be required to detect a significant difference in male infertility after mesh repair. Furthermore, such a study would only provide valid results if based on young men with bilateral hernias. We believe that the discomfort for the men participating in such a study (including very personal tests) would make inclusion very difficult. Taking all these aspects into account, we believe that conducting a randomized study is not the way to go. It is our opinion that the present study, based on register data, together with our previous prospective study[13] provide strong evidence that groin hernia surgery using mesh does not cause any increase in the incidence of, nor any clinically important risk for, male infertility.

We conclude that operative treatment for male groin hernia using mesh techniques may continue to be performed without major concern about the risk for male infertility.

This study was approved by Umeå Ethics Review Board.

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