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The importance of pseudocapsule preservation during hysteroscopic myomectomy

Andrea Tinelli[a,b,*], Alessandro Favilli[c], Ricardo Basil Lasmar[d], Ivano Mazzon[e], Sandro Gerli[c], Xiang Xue[f], Antonio Malvasi[g,b]

[a] Department of Obstetrics and Gynecology, Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy, Vito Fazzi Hospital, P.zza Muratore, Lecce, Italy
[b] Laboratory of Human Physiology, Phystech BioMed School, Faculty of Biological & Medical Physics, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia
[c] Department of Surgical and Biomedical Science, Santa Maria della Misericordia Hospital, University of Perugia, Italy
[d] Department of Surgery, Federal Fluminense, University, Av Marques do Paraná 303, Centro, Niterói, Rio de Janeiro, Brazil
[e] Endoscopic Centre, Clinica Nuova Villa Claudia, 00191 Rome, Italy
[f] Department of Obstetrics and Gynecology, Second Affiliated Hospital of Xi'an, Jiaotong University, Xi'an, China
[g] Department of Obstetrics and Gynecology, GVM Care & Research Santa Maria Hospital, Bari, Italy

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ABSTRACT

Minimally invasive techniques for myomectomy are based on the rationale of preserving the myometrial integrity, in order to spare muscular and fibro-neurovascular myometrial fibers and ensure complete and bloodless myoma removal. Post-operative myometrial vascularization is crucial in injured muscle regeneration. The post-surgical myometrial healing is needful for uterine reproductive function. Neurotransmitters and neurofibers were analyzed in the myoma pseudocapsule surrounding fibroid. They activate signaling molecule synthesis and release which, in turn, promote cell activation and induce muscle regeneration and growth. Pseudocapsule damage during myomectomy may lead to a reduction of neuropeptides and neurofibers at the hysterotomic site, to a poor physiological myometrial healing, with more fibrosis due to hypoxia, ischemia and necrosis.

These pathophysiological events cause deficit in myometrial neurotransmission, muscular impulse and contractility, with ultimately impaired uterine muscle function during pregnancy, labor and delivery. Hence, during myomectomy, all manipulations should be performed as precisely and bloodlessly as possible, avoiding extensive, high wattage diathermocoagulation or excessive tissue manipulation or muscular trauma. Any iatrogenic pseudocapsule damage may alter neurotransmitter function during successive myometrial healing, impacting negatively on uterine repair and on eventual pregnancies. Hence the reasoned myomectomy on a biological basis, the "intracapsular myomectomy", satisfied these surgical and physiological requirements. It was described precisely and firstly by the hysteroscopy, with the image magnification of the preservation of the myoma pseudocapsule. The "intracapsular hysteroscopic myomectomy" demonstrated the safe and effective removal of submucous myomas with intramural development. It allowed to completely remove the myoma in one or two surgical steps, saving the pseudocapsule and the surrounding healthy myometrium. The respect of the myometrium and the reduced thermal injury, a part the excellent outcomes in terms of surgical complications prevention, post-surgical fibrosis and intrauterine synechiae reduction, highlighted the physiological development of a successive pregnancy, without any myometrial complications during pregnancy, labor and delivery.

Introduction

The most common female genital tract pathology is the uterine myoma or fibroid, with a prevalence ranging from 5.4% to 77%, according to age, ethnicity and diagnostic method [1]. Fibroids are one of the major causes of infertility, apart from being a source of abnormal uterine bleeding and pelvic pain. Even though most of

* Corresponding author. Tel.: +39/339/2074078, Fax: +39/0832/661500.
E-mail addresses: andreatinelli@gmail.com (A. Tinelli), alessandrofavilli.mail@gmail.com (A. Favilli), ricardolasmar@gmail.com (R.B. Lasmar), mazzon.ivan52@gmail.com (I. Mazzon), gerli@unipg.it (S. Gerli), xue.xiang@yahoo.com (X. Xue), antoniomalvasi@gmail.com (A. Malvasi).

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fibroids are asymptomatic, they are associated with a higher risk of complications during pregnancy, labor and delivery [2]. Surgical enucleation by myomectomy is the main option to treat symptomatic fibroids. The choice of the vaginal, abdominal or hysteroscopic approach depends on fibroid site, number and size [3]. Myomectomy must ensure the complete and bloodless myoma removal sparing the muscular and fibro-neurovascular myometrial fibers. Hence, the attention is currently focusing on minimally invasive techniques and myoma pseudocapsule preservation [4].

Physiology of uterine muscle repair

After the first weeks after myomectomy, myometrium generally requires a physiological healing to restore the uterine biology. The damaged muscle in the human body can itself promote the signaling processes that activate its regeneration. Then, after membrane damage, neurotransmitters and neurofibers synthesized and released signaling molecules that promoted cell activation and induced muscle regeneration and growth [5].

The "injury-repair-regeneration" sequence is associated with a functional muscle reconstitution within days or weeks [6]. Since vascularization of the injured muscle area is crucial for regeneration, the new vascular network in the myometrial fovea (where the fibroid was located) was the first sign of tissue repair, as a prerequisite for subsequent morphological and functional uterine healing. In neoangiogenesis, new capillaries sprouted from surviving blood vessel trunks and extended towards the myometrial fovea center, thus supplying adequate oxygen and aerobic energy metabolism for myometrial repair [7]. Neuropeptides and neurotransmitters also play a main role in wound healing. In fact, the nervous system and its neurotransmitters, such as Substance P (SP), Vasoactive Intestinal Peptide (VIP), neuropeptide Y (NPY), Oxytocin, Vasopressin (VP), PGP9.5, calcitonin gene-related peptide (CGRP), growth hormone-releasing hormone (GHRH), were observed to mediate inflammatory processes and healing [8]. After cervical surgery, for example, the oxytocin neurofibers were detected at the cervix and at a higher level, in the cervical-isthmus area, leading to speculation that they impacted positively on the reproductive system and sexual disorders [9].

In myometrial scar biology, the spared peptides enhanced healing at the hysterotomic site. Many neuropeptides were detected in the myoma pseudocapsule and were transported to tissues by the neurovascular network. Consequently, the myoma pseudocapsule works biologically like a neurovascular bundle, as a neurofibrovascular structure rich in neuropeptides and neurofibers [10–12]. The literature has not clarified whether myoma-related mechanical and inflammatory effects on the myometrium sustained the pseudocapsule vasculature network, or whether it was produced by "neoplastic-type", neoangiogenesis, due to fibroid growth or even to muscle and tissue healing [13]. During myomectomy or caesarean section (CS) in humans, difficulties in obtaining serial samples of the hysterotomic scar are the main obstacles to advancing biological and surgical knowledge. Indeed, the uterine wound remodeling processes after myomectomy (and CSs) should be clarified by ultrasound or magnetic resonance imaging (MRI) monitoring [14].

The dynamic and interactive process of wound healing involves three complexes and overlapping biological phases: inflammation, tissue formation and remodeling. Neuromodulators, angiogenetic factors, neuropeptides, blood cells, extracellular matrix, and parenchymal cells all have also an important role as healing catalysts [15]. Additionally, biochemical growth factors in the pseudocapsule vessels, promoters of intense angiogenesis in the pseudocapsule area, are most probably promoted by the fibroids themselves [16]. Moreover, the hormonal and pharmacological impacts of drugs on the pseudocapsule need to be largely analyzed and clarified, as their role is not yet clear either in fibroid growth or in compromising the pseudocapsule biology [17]. Finally, the pre-operative therapy and the post-operative follow-up might also need to be targeted in order to preserve uterine biology as much as possible [18,19].

The surgical physiology of "intracapsular myomectomy"

During the "intracapsular myomectomy", the fibroid is removed sparing, as much as possible, its pseudocapsule, the surrounding neurovascular bundle rich of neuropeptides and neurofibers. The neurovascular bundle was firstly detected in urological laparoscopy during radical prostatectomy. What has been biologically proven after the preservation of the prostate neurovascular bundle prostate was usefully translated into the gynecological field, on fibroids [13]. During dissection near prostate neurovascular bundles, the high wattage diathermocoagulation for hemostasis is always avoided, as for the possible injury of cavernous nerve function in the canine model, with a deterioration of sexual function pelvic nerves after prostatectomy [11,13,20]. These important steps in prostatic capsule sparing and the physiological role of nerve-sparing techniques in prostatectomy were translated to pseudocapsule sparing during myomectomy [13].

Hence, during the "intracapsular myomectomy", as already described [8,21,22], the surgeon stretches and extracts the fibroid from its muscular fovea and detaches it directly from the adjacent myometrium, avoiding to damage to the surrounding fibromuscular skeleton and fibrous bridge break-up. Generally, in the laparoscopic/laparotomy or hysteroscopic settings, enucleation of each fibroid needs to be gently performed firstly to enhance and improve post-surgical myometrial healing and, later, to promote the restoration of uterine anatomy and biology [23,24]. For the above-mentioned biological reasons, the fibroid pseudocapsule neurovascular bundle should always be protected and spared during myomectomy. It should be always avoided the extensive and high wattage diathermocoagulation on fibroid site, the excessive tissue manipulation and muscular trauma [8–14]. Myomectomy with pseudocapsule damage may lead to the following surgical sequelae: 1) fewer neuropeptides and neurofibers at the hysterotomic site, with a negative impact on physiological myometrial healing; 2) an increase in the fibrotic process at the hysterotomic site, due to hypoxia, ischemia and necrosis; 3) a deficit in either myometrial neurotransmission or muscular impulse and contractility, with ultimately impairments in uterine muscle function. Hence, the myomectomy-related neurovascular bundle injury could produce an impaired myometrial healing and an abnormal myometrial biology and functionality, with negative effects on a subsequent pregnancy, labor and delivery, with the possibly even of a dramatic uterine rupture [25].

The general surgical recommendations during myomectomy indicate to perform all manipulations as precisely and bloodlessly as possible, to maintain pseudocapsule integrity and always sparing the neurovascular bundle.

Intramural and subserosal intracapsular myomectomy

During the "intracapsular myomectomy", laparoscopic approach is different to laparotomy. The laparoscopic intracapsular myomectomy (LIM) (Fig. 1) promotes and supports the pseudocapsule sparing and the musculature preservation thanks to the hemostatic CO2 pressure role. The increased intra-peritoneal pressure due to CO2 insufflation occludes pseudocapsule small blood vessels and capillaries, reducing intra- and post- operative blood loss. Moreover, the advantages of laparoscopy included less bladder pain after Foley catheter removal, fewer patients requiring pain relief medication and shorter hospital stays. Compared with

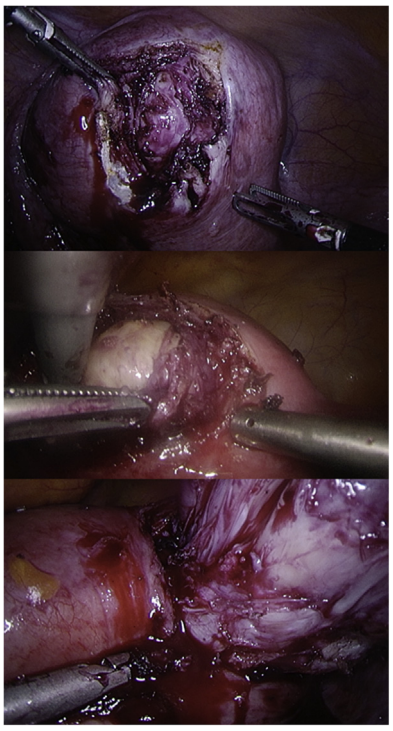

Fig. 1. Laparoscopic intracapsular myomectomy: from top to bottom, the phases of enucleation of the fibroid from the uterus, by preserving the myoma pseudocapsule.

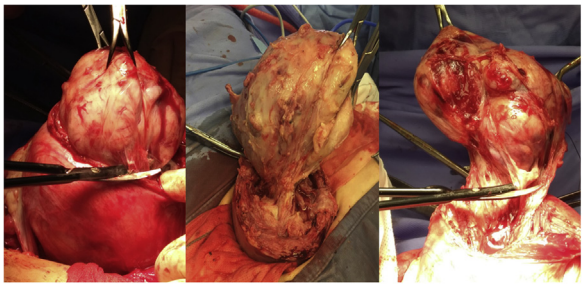

Fig. 2. Laparotomic intracapsular myomectomy: from right to left, the phases of the fibroid enucleation from the uterus, by identification and cutting with bipolar scissors, for the preservation of the myoma pseudocapsule.

open myomectomy (Fig. 2), LIM also improved short-term outcomes slightly in terms of post-operative fever, myometrium scar hematomas, ileus and antibiotic treatment [26,27]. These are the reasons why the less traumatic endoscopic micromanipulations contribute to the beneficial outcomes of a LIM. The LIM technique is generally the following. The visceral peritoneum is incised, along the midline longitudinal plane of myometrium, by monopolar scissors, a Harmonic scalpel or crochet needle electrode (all in low energy or wattage). The myoma pseudocapsule is easily recognized during dissection, gently cut to expose the myoma surface, which must be further highlighted by atraumatic clamps or irrigator cannula. The "cleavage plane" (between myoma and pseudocapsule) identification is a crucial step, to avoid the muscular fibers damaging and to ensure low blood loss during and after surgery. Bipolar clamps, a Harmonic scalpel, and hook electrode or monopolar scissors, always at low wattage (not over 30 W), selectively achieve hemostasis of small vessel bleeding during the "cleavage plane" dissection. The unseen part of the fibroid into the myometrium during myomectomy, the so-called "myoma base", is gradually exposed, as the connective myoma-pseudocapsule bridges are coagulated during fibroid traction. This method is usually associated with complete, minimally traumatic fibroid removal from its pseudocapsule, minimal blood loss and pseudocapsule sparing.

Hysteroscopic intracapsular myomectomy

In 1976 the advent of hysteroscopic myomectomy, which was first reported by Neuwirth et al. [28], radically changed submucous fibroid treatment. Laparotomy was abandoned, so as surgical outcomes significantly improved. Ideally, hysteroscopic myomectomy should be a simple, well-tolerated, safe and effective procedure, preferably accomplished in a single surgical step [29]. Even though it constituted the gold standard in submucous myoma treatment [29], it was associated with an high risk of surgical complications. They range from cervix laceration to potentially fatal uterine perforation with electrical loop or clinical intravasation syndrome, one connected to the other [30–32].

Assessing the rate of these surgical complications is rather complex, as they are related to disease features, surgeon expertise and techniques [33]. Wamsteker et al [34] and then Lasmar et al [35], investigated and evaluated submucous myoma features that influenced surgical outcomes. Intracavitary myomas with an intramural extension of 50% or more were always a challenge in hysteroscopic myomectomy, as they were linked to an increasing risk of intraoperative complications and to the need for a multiple-step procedure to complete the operation [36,37]. And the risks of surgical complications are even higher with multiple diagnosed fibroids [38]. In hysteroscopic myomectomy slicing-related issues, underlie all intraoperative complications, such as bleeding, uterine perforation using electrical loop and the clinical intravasation syndrome [39]. This is probably because even today, the resectoscopic slicing is still the most widely used technique for treating submucous fibroids. Indeed, the standard slicing technique, even in expert hands, makes very difficult the myometrial and pseudocapsule sparing. During the intramural myoma removal, the "pseudocapsular tissue" (Fig. 3) should be always visualized over the entire resected area and in its uterine fovea, to distinguish myoma tissue, pseudocapsule and healthy myometrium (Fig. 4). The traditional electrical loop's direct-action during slicing alters the dissection of anatomical planes, so that it is almost impossible to avoid injuring myometrial fibers. The pseudocapsule and surrounding healthy myometrium injury may be both direct (by cutting) and indirect (by thermal damage). Furthermore, during hysteroscopy, surgical trauma to healthy uterine wall tissue was reported to play a role in successive synechiae development [36,38–40]. In order to overcome the limits of standard slicing of the myometrial portion of submucous myomas, several techniques were developed in the past decades. Their main objective was the successful myoma detachment to facilitate the slide from the myometrium into the uterine cavity. Some authors took advantage of uterine contractions as induced by manual massage [41], by drugs [42–44], by changing intrauterine pressure [43] or by a combination of multiple techniques [45,46]. Other authors reported intramural myoma detachment by means of electrical incision of the fibro-connective bridges, which anchored the myoma to the pseudocapsule [47,48]. In 1995, the cold loop hysteroscopic myomectomy was the first of these techniques to be described [49]. In this innovative treatment, the myoma standard slicing, which was essentially the surgeon's use of electrical power to remove the myoma, was abandoned. Surgeons switched to mechanical myoma enucleation from the pseudocapsule, taking advantage of physiological myometrium contractions. The cold loop disconnected the fibro-connective bridges anchoring the fibroid to its pseudocapsule using mechanical method (Fig. 5). Thus, it permitts the intramural myoma enucleation, without damage to the surrounding healthy myometrium. Applying the

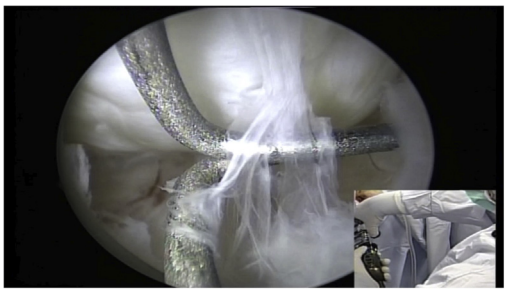

Fig. 3. Hysteroscopic myomectomy by intracapsular technique: highlighting of the pseudocapsule tissue by equatorial loop (cold loop technique).

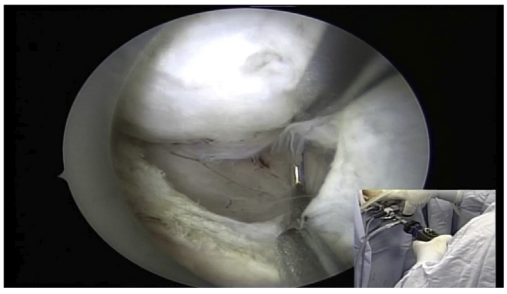

Fig. 4. Hysteroscopic myomectomy by intracapsular technique: highlighting the myoma, at the top, of the myometrium, at the bottom, of the pseudocapsule, in the center.

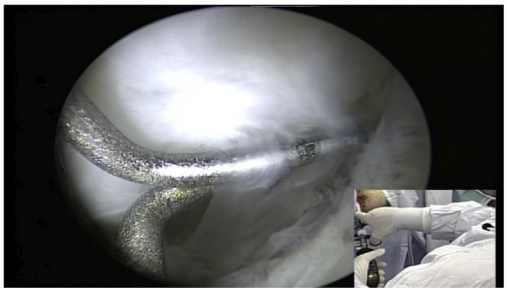

Fig. 5. Intracapsular hysteroscopic myomectomy: the cold loop mechanically disconnected the fibro-connective bridges anchoring the fibroid to its pseudocapsule.

cold loops between myoma and pseudocapsule (Fig. 6), surgeon prevented electrical loop-related uterine perforation and serious injury to abdominal organs or vessels. Even if the cold loops should cause perforation, damage was like the Hegar' dilators injury. Myometrium sparing allowed uterine contraction, which enhance the intramural myoma slide into the uterine cavity and increased the free myometrial margin thickness [50]. Moreover, uterine contraction and myometrial muscular fiber sparing lowered the risks of bleeding and distension medium absorption, enhancing the chances of accomplishing a single step hysteroscopic myomectomy [8,36,37]. Pseudocapsule sparing during hysteroscopy also promoted myometrial healing and prevented fibrotic scarring, intrauterine adhesions and dramatic complications, such as uterine rupture [51]. Although not considered the treatment of choice, the cold loop hysteroscopic myomectomy seemed to be a reasoned and biological option for treating submucous myomas. It correctly distinguished anatomical planes, safeguarded myometrium and pseudocapsule anatomy and functional integrity and ensured a safe, effective procedure, which, in many cases, was accomplished in a single-step procedure [51,52].

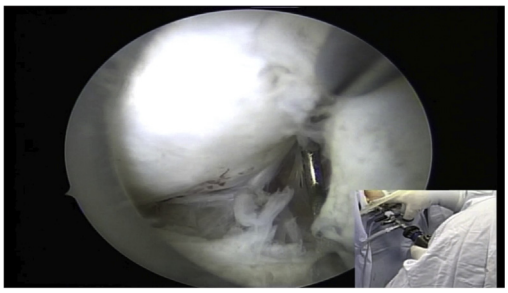

Fig. 6. Hysteroscopic myomectomy by intracapsular technique: the cold loop separates the pseudocapsule into fibroid by highlighting the myoma fovea in the myometrium, in a bloodless method.

Pregnancy outcomes of hysteroscopic intracapsular myomectomy

Patients in childbearing age undergoing hysteroscopic myomectomy are generally seeking pregnancy. A surgical or biological complication in such women could have a double negative effect.

As previously described, the intracapsular myomectomy allows to mechanically enucleate the myoma to the myometrium sparing pseudocapsule. This reduces the risk of causing possible damage to the myometrium, with negative effects on myometrial physiology and the surrounding endometrium. The myomectomy sparing pseudocapsule has already been associated with very few surgical complications and enhanced healing, and good fertility rates and delivery outcomes [36]. Literature stated that the safety of pregnancies successive to hysteroscopic myomectomy is greatly improved by the risk reducing of thermal damage to the myometrium and surrounding tissues [53–55], which are the basic event in the uterine pathophysiology during the successive pregnancy [56]. Moreover, scientific reports described uterine rupture during pregnancy after accidental uterine perforation by thermal loop [57–59]. Mazzon et al never recorded a uterine rupture following cold loop hysteroscopic myomectomy [38,60]. Leone et al. reported a pregnancy rate of 45% in a group of infertile patients treated by cold loop myomectomy; authors reported excellent pregnancy outcomes by intracapsular technique, treating also extreme cases [61].

Conclusions

The discovery of the fibro neurovascular structure of few millimeters of size, the myoma pseudocapsule, rich in neurotransmitters together with evidence of dedicated angiogenesis, neurofibers and neuropeptides, prompted its systematic preservation during myomectomy [62]. Pseudocapsule sparing ensured myometrium integrity around the fibroid fovea and enhanced post-operative myometrial healing. The cold loop hysteroscopic myomectomy demonstrated the safe and effective removal of submucous myomas with intramural development, also in one surgical step. This technique still needs to be verified with the new instruments that use myomas morcellation during hysteroscopy [63], as it could even be performed avoiding general anesthesia [64]. The myometrial respect during fibroid enucleation, added to the reduced thermal injury, showed excellent outcomes in terms of surgical complications prevention, post-surgical fibrosis and intrauterine synechiae reduction. The intracapsular myomectomy, associated to the endoscopic "microsurgical" magnification, enhances the physiological development of a successive pregnancy without any myometrial complications. The myomectomy with pseudocapsule sparing is a safe and feasible minimally invasive technique, which should become a routinely surgical method in all reasoned myomectomies, especially in patients wishing a successive pregnancy.

Author Contributions

AT, AF and AM conceived and were responsible for carrying out the study; AT, AF and BL performed data collection; AT, AF and SG writing the final manuscript; BL, IM and SG critically revised the manuscript. XX revised second manuscript. All the authors reviewed, edited, and approved the final submission.

Study Founding

None.

Declaration of Competing Interest

None.

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None.

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