Microsurgical principles and postoperative adhesions: lessons from the past

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“Microsurgery” is a set of principles developed to improve fertility surgery outcomes. These principles were developed progressively based on common sense and available evidence, under control of clinical feedback obtained with the use of second-look laparoscopy. Fertility outcome was the end point; significant improvement in fertility rates validated the concept clinically. Postoperative adhesion formation being a major cause of failure in fertility surgery, the concept of microsurgery predominantly addresses prevention of postoperative adhesions. In conclusion, the principles of microsurgery remain fully valid as the cornerstones of reproductive microsurgery, whether performed by means of open access or laparoscopy. (Fertil Steril 2016;106:1025–31. ©2016 by American Society for Reproductive Medicine.)

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Surgical procedures in the peritoneal cavity, regardless of the access mode, frequently generate postoperative adhesions. Surgeons have been aware of this for more than a century: A German surgeon, K. Baisch, in an article published in 1905, discussed some of the causes of adhesion formation: “These experiments show the dire consequences of leaving blood in the peritoneal cavity, whenever the serosa is also damaged … Blood may find the smallest area denuded of epithelium, whereon it may begin to clot and build up fibrin” (1).

The incidence of sexually transmitted diseases increased significantly from the early 1960s onward. Infections are the most common cause of damage to the fallopian tubes. Impaired tubal function leads to infertility and/or tubal pregnancy (2–5). This was the era when the bulge of the baby boomers became pubertal, coincident with the liberal availability of nonbarrier contraceptives, both oral contraceptives and intrauterine devices, and a more permissive sexual behavior (6). Epidemiologic studies revealed a doubling or more of both infertility and ectopic pregnancy from 1960 to 1975 (7–10).

In parallel, over the same period, the character of sexually transmitted disease was transformed from clinically flamboyant to occult. Most infections were caused by Chlamydia, which is an obligate intracellular organism with virus-like properties associated with subclinical “silent” salpingitis. Subsequent observations demonstrated that >30% of women with post–pelvic inflammatory disease tubal damage to the fallopian tubes and with pelvic and often hepatic adhesions did not have a history of any symptoms (11–14).

Tubal-factor infertility results also from the misdiagnosis or delayed...
diagnosis and treatment of acute abdominal and pelvic conditions in young and/or reproductive-age women, such as pelvic inflammatory disease, appendicitis, ectopic pregnancy, etc. It is also caused by surgical procedures that are unnecessary or unnecessarily extensive and/or traumatic, resulting in damage to or loss of normal reproductive organs and development of pelvic and periadnexal adhesions [15].

REPRODUCTIVE SURGERY IN THE SIXTIES

The causes of postoperative adhesions are multiple. The major one is direct surgical trauma to the operative site and to the remainder of the peritoneal cavity. Additional factors include ischemic and thermal injury, damage to the mesothelial layer of the peritoneum by desiccation or trauma with sponges or instruments, bleeding and blood left in the peritoneal cavity, introduction of foreign bodies, the use of reactive sutures, and, obviously, postoperative infection.

In the 1960s and 1970s, nearly all abdominal and pelvic operations were performed through a laparotomy. Large sponges were used to retract the bowel; the peritoneal cavity was exposed to the room atmosphere and to the heat of the lights illuminating the operative site. Intraoperative irrigation was rarely used, and when it was, saline solution was used. This also applied to lavage, when performed, at the close of the procedure. Reconstructive tubal surgery was largely limited to salpingostomy and adhesiolysis, for hydrosalpinx and periadnexal adhesions, sequel of salpingitis usually caused by sexually transmitted organisms. To keep the tube open, a silastic device, the “Mulligan hood,” was attached, with the use of three single sutures, to the edges of the stoma created at the distal end of the tube [16]. It was necessary to perform a subsequent laparotomy 3 months later to remove the silastic devices. I have vivid recollections of the frustration and disappointment I felt, assisting as resident at second laparotomy, at finding extensive adhesions in the abdomen with bowel, omentum, and the internal genitalia adherent to each other. Extensive adhesiolysis and separation of the involved structures was often necessary to expose the fallopian tubes and remove the prosthetic devices. It seemed evident that adhesions would re-form and that they were likely one of the reasons for the relatively poor reproductive outcome.

That periadnexal adhesions adversely affect fertility has been clearly demonstrated. A Canadian controlled study investigated treatment-dependent and treatment-independent pregnancies in 147 patients with periadnexal adhesions diagnosed during an initial diagnostic laparoscopy (patients with tubal occlusion and endometriosis were excluded) [17]. Sixty-nine of these women underwent microsurgical salpingo-ovariolysis; the other 78 were not treated and served as control subjects. The intrauterine pregnancy rate was 42% among the 69 operated women compared with only 12% in the control group. Furthermore, in both groups the pregnancy rate was adversely affected by the extent of adhesions. The deleterious effect of periadnexal adhesions on fertility has been demonstrated also by a study on laparoscopic salpingostomy from Greece [18]. We reported a series of laparoscopic salpingo-ovariolysis composed of 90 patients, whose primary cause of infertility was periadnexal adhesions. In 40 (44%) of these 90 women, the cause of periadnexal adhesions and resulting infertility was secondary to previous surgical procedures, such as ovarian surgery, myomectomy removal of ectopic pregnancy, appendectomy, etc. [19].

By 1971 [20] several factors that induce intrauterine adhesion formation had been demonstrated in nonhuman animal experiments: peritoneal injury [20], the coalescence of two injured and closely apposed serosal surfaces [21, 22], the importance of fibrin and fibrinolytic mechanisms [23, 24], that blood allowed to clot becomes firmly adherent to a desiccated serosal surface [1, 20, 25, 26] whereas heparinized or defibrinated blood does not adhere and does not cause adhesions [27, 28], and the deleterious effects of ischemia [29], of talcum powder that usually covered surgical gloves [30, 31], of gauze sponges [20], and of the toxicity of saline solution [20], inhibition of bowel peristalsis because of drugs [32, 33], and even individual susceptibility to form adhesions [34].

MICROSURGERY

Microsurgical principles were introduced into gynecology in the late 1960s and early 1970s. After experimenting on eight monkeys, a series of albino rats, and a controlled study on patients operated on for a tubal gestation, Swolin observed that "intraperitoneal application of a single dose of 2,000 mg hydrocortisone acetate at the end of the operation prevents or decreases the formation of postoperative adhesions" [35, 36]. He reported on 50 “fertility operations” with the use of “a type of microsurgery asatraumatic and bloodless as possible” along with the insertion of 2,000 mg cortisone acetate into the peritoneal cavity before closure [37]. The 50 cases comprised 33 salpingostomies, ten salpingolyses, five uterine implantations, and two myomectomies with coagulation of focal endometriosis. In the whole group of 50 patients, he reported a total pregnancy rate of 36%; of those, 22% were ectopic gestations and 78% were intrauterine (overall, there were 22% live births, 2% abortions, and 4% ongoing pregnancies at the time of reporting).

Among the 33 women submitted to salpingostomy, nine (27%) became pregnant; three (9%) of these 33 women had ectopic gestations and six (18%) had intrauterine pregnancies, with five (15%) delivered and one pregnant at the time of reporting [37]. These are modest outcomes for the whole group, which included ten cases of salpingolysis, as well for the salpingostomy group. These outcomes were similar to those reported with more traditional techniques, which was surprising.

Curious to find out more, I introduced myself to Professor Swolin at the IFFS World Congress in May 1968. I was fortunate to be accepted to spend February and March 1969 at the Sahlgrenska University Hospital in Gothenburg, Sweden, where he worked. During my stay of 2 months, only four cases were performed, three of which were salpingostomies necessitating adhesiolysis, and one a bilateral tubouterine implantation. I assisted him in all four operations. He used magnifying loops to operate; I did as well. He was meticulous.
and operated with great care. The tubouterine implantation was performed with the use of the Shirodkar technique, which includes a fundal hysterotomy incision from one cornu to the other and the use of a polyethylene prosthesis designed to keep the implanted portions of the tubes open. This device is removed 6 weeks later with the use of a Gräfenberg hook introduced through the cervix (38, 39). Each operation, with two breaks for hydration and nourishment, took 5–6 hours.

In 1969, reconstructive surgery was the only realistic option for the treatment of infertility due to tubal and peritoneal factors. This was to remain the case until 1990, when the rate of live births per initiated in vitro fertilization (IVF) cycles reached 12% in the USA (40). There was work to do.

Back in Vancouver, we initiated the development of a reproductive microsurgery program, starting by taking a course to learn to anastomose a 1-mm vessel with the use of 10–0 sutures. A Zeiss operating microscope was available and the nurses were on board. Initially, we used ophthalmic microsurgical instruments and homemade glass rods to mobilize bowel and retract tissue. Eventually, when we gained some recognition, the Martin company (Germany) developed our own instruments which were more appropriate to work on the reproductive organs. On our request, Ethicon produced a 3/8 circle, 130-µm, 3.7-mm taper-cut needle, swaged on 8–0 Vicryl suture, for use in tubal microsurgery. Collaborating with Valleylab, we developed a handle for their electrosurgical unit that had an appropriate design, weight, and length, included a rocker switch allowing fingertip control for cutting and coagulation, and was able to accommodate both regular and microelectrodes (41).

We reviewed the data on adhesion formation available at the time, as summarized in a paragraph above. In addition to reducing trauma at the site of surgery, we had to develop a system that decreased injury and inflammation in the peritoneal cavity. The microsurgical tenets were developed over time with the use of nonhuman animal experiments and clinical observations, which included systematic second-look laparoscopies, performed 8–12 weeks after the initial surgery. These postoperative observations drove the adjusting and improving of practice and techniques. We performed second-look laparoscopies during the initial 4–5 years and abandoned their systematic use when the findings, especially the paucity of adhesions, proved to be better than expected.

With experience we added, deleted, or changed certain aspects. For example, we abandoned the use of prosthetic devices, such as intratubal stents, early on. Initially, we used peritoneal grafts to cover areas denuded of peritoneum, as suggested by Palmer (42), but realized that not infrequently they undergo necrosis and often cause adhesions, so we abandoned it altogether. The same applied to postoperative hydro-perturbation, which was very much in vogue at the time (43–45). We improved the techniques of various procedures, starting initially with tubotubal anastomosis. The magnification and the ease of operation afforded by the operating microscope allowed us to assess the tissues and perform an anastomosis in two layers with the use of the fine instruments and sutures described above and to obtain significantly improved results in terms of intrauterine pregnancies and live births (46–49).

Subsequently, we used a totally new approach for the surgical treatment of pathologic cornual occlusion. Instead of a tubouterine implantation, which requires a hysterotomy incision from one cornu to another, use of a prosthesis, and a cesarian section for delivery, we developed a more physiologic approach, which can be performed by microsurgery: a tubocornual anastomosis. This approach maintains the integrity of the uterus and the cornu and permits the patient to labor and deliver normally, except in the presence of obstetrical or other pertinent complications (46, 48, 49). Clinical work in Vancouver commenced in the spring of 1970, and we reported our techniques and results for the first time at the 8th World Congress of Fertility and Sterility in Buenos Aires, Argentina, in November 1974 (50).

Microsurgery has been erroneously defined as “surgery under magnification.” In fact, magnification is only one aspect of microsurgery, which embraces a broad concept of tissue care designed to minimize tissue injury, prevent postoperative adhesions, and improve outcomes. The basic principles of microsurgery include: 1) delicate handling of tissues and judicious use of electrical or laser energy; 2) frequent intraoperative irrigation of exposed tissues with heparinized lactated Ringer solution at room temperature (5,000 IU heparin per liter, to which we also added 100 mg cortisone succinate) to prevent desiccation of the peritoneum and decrease clotting of blood in the peritoneal cavity; 3) prevention of foreign body contamination of the peritoneal cavity: operating gloves thoroughly washed to remove the talcum before the start of the procedure (there were no talcum-free gloves at the time) and the use of lint-free surgical pads which were soaked in the heparinized Ringer solution before use; 4) meticulous pinpoint hemostasis that minimizes adjacent tissue damage: achieved with the use of a microelectrode or a very fine bipolar forceps (the microelectrodes are insulated, have a bare conical tip of 100 µm, and can also be used for cutting without touching the tissue); 5) identification and use of proper cleavage planes; 6) complete excision of abnormal tissues; 7) excision and removal of broad adhesions (shallow adhesions are simply divided mechanically); 8) precise alignment and approximation of tissue planes; 9) performing a thorough lavage with the use of heparinized Ringer solution at the end of the procedure to remove any blood clots, foreign body, or debris that may be present in the peritoneal cavity; 10) leaving 300–500 mL Ringer solution, to which 500–1,000 mg hydrocortisone succinate is added, in the peritoneal cavity before total peritoneal closure (we elected to use hydrocortisone succinate because it is water soluble, as opposed to hydrocortisone acetate, used previously by Swolin (35, 36), which is not water soluble and leaves a yellowish residue in the peritoneal cavity); and 11) use of magnification, as necessary: permitting prompt identification of abnormal morphologic changes, recognition and avoidance of surgical injury, and application of the preceding principles with the use of appropriate fine instruments and suture materials. The whole procedure is performed with the use of mechanical instruments assisted by electrosurgery (45, 46).

With open cases, at the end of the procedure an ilioinguinal nerve block is performed (47). This enables the patient to move more easily and to require less analgesic.
medication, because bowel motility had been shown to be important in adhesion prevention. To reduce inflammation, a 100-mg Voltaren suppository is inserted before the patient is anesthetized and after the surgery. In addition, the patient is administered one or two doses of dexamethasone after surgery.

We did not use barriers for three reasons. First, the second-look laparoscopies demonstrated such a paucity of postoperative adhesions that added value of a barrier was limited and difficult to demonstrate. Furthermore, during the developmental phase of microsurgical principles there were no barriers of proven efficacy available. With the concept of keeping affected surfaces separated, we used temporary suspension. If the uterus had been adherent posteriorly, or the ovary and/or fallopian tube to the fossa ovarica or pelvic sidewall, we performed a ligamentopexy, ovariopexy, or salpingopexy (42). Later we were asked to participate in a multicenter trial of Interceed (oxidized regenerated cellulose), but we were not permitted to perform a preliminary trial on laboratory animals, which was our condition to participate. Much later we found in rats that pretreatment with 0.45% hyaluronic acid solution (HA) in phosphate-buffered saline solution (Genzyme), before onset of surgery prevented postoperative adhesions better than application at the end of the procedure, and better than phosphate-buffered saline solution alone applied similarly. HA appeared to reduce adhesions by coating the peritoneal surfaces and thus decreasing the extent of tissue injury (48). We were very excited when an HA membrane became available, hoping that it would prove to be an excellent barrier. Unfortunately, this was not to be; 3 hours later none of the HA membranes remained adherent to the injury site: The membranes had converted to a gelatinous form and were floating in the peritoneal cavity (49).

Thus, microsurgery is a surgical philosophy as much as a technique: a delicate surgical approach designed to minimize peritoneal trauma and tissue disruption, and to prevent postoperative adhesions while increasing the accuracy of the procedure and improving the outcome. It is evident that this progressive development did not comprise randomized clinical trials (RCTs) for each element of these surgical principles separately; we relied on clinical feedback with the use of second-look laparoscopy and pregnancy outcomes.

**LAPAROSCOPIC REPRODUCTIVE SURGERY**

The microsurgical technique was initially used for open reconstructive tubal surgery, yielding greatly improved outcomes (46, 50–52), and soon after in other types of reproductive procedures as myomectomy, ovarian cystectomy, endometriosis, etc.

Recognizing that laparoscopy provided a surgical access route, we commenced to apply the same microsurgical principles in patients whose infertility was caused by distal tubal disease, initially salpingo-ovariolysis and soon after fimbrioplasty, salpingostomy, and tubal pregnancy. Although procedures were performed by mono-ocular vision viewing the operative field directly through the ocular of the laparoscope, it was possible to work with two hands, while the scope was held steadily in place by the assistant, and to treat the patient during the initial diagnostic laparoscopy. Realizing that laparoscopic access proved to yield similar results to those obtained with the use of open surgery, early on we recommended the use of laparoscopic access for surgical treatment of such conditions in papers published from 1975 to 1978 (53–56).

Expansion of operative laparoscopy and its use for increasingly more complex procedures in the mid-1980s was made possible by technical progress, especially development of small lightweight high-definition cameras and high-definition television monitors. This was tremendous progress, because it made it possible to view the operative field through one or more television monitors, enabling the surgical team to work harmoniously (57). In those heady days of laparoscopic surgery revolution, the microsurgical techniques and tenets were largely forgotten or ignored. The belief was that adhesions would no longer be a problem as long as the procedure was done by laparoscopy. In 1987, we designed an nonhuman animal study: A standard trauma was inflicted through the serosa and superficial muscularis of one of the uterine horns with the use of either laparotomy or laparoscopy and a microsurgical technique in both groups (58). Postoperative adhesions were assessed 2 weeks later by means of second-look laparotomy, during which the adhesions involving the uterine horn were lysed with the use of microscissors under the magnification of an operating microscope. The resulting raw patches on the uterine surface were stained with methylene blue solution and measured with the use of a millimeter-graded transparency and expressed in mm². The mean surface area of uterine adhesions was 4.29 mm² in the laparotomy group versus 8.88 mm² in the laparoscopy group (58). This outcome was surprising, because we expected the contrary. Other experimental studies and clinical observations demonstrated that the extent and type of postoperative adhesions at the primary operative site are similar regardless of the mode of access, laparotomy or laparoscopy. However, this was not understood at the time.

With the subsequent expansion of laparoscopic surgery, most reproductive surgical interventions designed to restore fertility or to treat other pathologies in the reproductive tract were often performed by this access route and as part of a diagnostic laparoscopy. Thus, reproductive surgery became mainstream surgery, whereas microsurgical reproductive surgery was performed in specialized referral centers after diagnosis and referral. In the decade of the 1990s the successful outcomes of IVF doubled. In those days of laparoscopic surgical revolution and improved IVF results, the microsurgical tenets were largely forgotten, probably owing to the belief that adhesions were no longer a problem and that IVF could back up a failed surgery.

Use of microsurgery in laparoscopic surgical access offers specific advantages. Suturing with fine sutures is easier after microsurgical training. In laparoscopy, operating within a closed peritoneal cavity eliminates the need to use surgical pads and decreases the potential for bacterial and foreign body contamination. It is possible to bring the distal end of the laparoscope close to the area of interest and achieve excellent illumination, visibility, and magnification. The pressure effect of the pneumoperitoneum diminishes venous oozing...
and permits spontaneous coagulation of minor vessels. Intraoperative irrigation permits keeping tissues moistened, exposing any bleeding vessels, and achieving precise electrosurgical hemostasis with the use of a fine electrode or bipolar forceps. However, these advantages would be eliminated with the use of crude instruments, large electrosurgical electrodes, and application of overzealous energy, which would result in increased local trauma and necrosis. With laparoscopic access, there is a reduction of haptic feedback; suturing, especially with finer sutures, is more difficult. Preliminary training in microsurgery improves these skills and makes the surgeon a more gentle operator and acutely aware of avoiding trauma. Currently, new equipment, instruments, and energy modalities are being used in laparoscopic surgery; the effects of these modalities need to be properly appraised.

DISCUSSION

It is evident that fertility-promoting surgery preferably should be done with the use of microsurgical principles. This is strongly endorsed by the American Society of Reproductive Medicine: “Only surgeons who are very facile with laparoscopic suturing and who have extensive training in conventional tubal microsurgery should attempt this procedure” [59]. The same applies to reproductive procedures such as myomectomy, ovarian cystectomy, endometriosis, etc., in adolescents and women of reproductive age.

Microsurgery has erroneously been considered to be merely surgery with a microscope and a series of rituals based on common sense. That its development was based on experimental evidence and clinical feedback by means of secondlook laparoscopies has not been appreciated to its full extent. The latter have become “ passé” since systematic repeated laparoscopies are no longer clinically acceptable.

If we were to consider the microsurgical principles as research data, the striking clinical similarity with our actual understanding of adhesion formation and prevention should not be unexpected. Indeed, recent scientific evidence has shown the importance of gentle tissue handling, of bowels and the entire peritoneal cavity, minimal surgical trauma and blood, avoiding desiccation, and the use of corticosteroids in the prevention of postoperative adhesions [60]. These findings confirm what was clinically known already. This also applies to the use of Ringer lactate instead of saline, which was known to be harmful to mesothelial cells [20], and cooling. Microsurgery did not advocate heating the irrigation fluid to 37°C; it was used instead at room temperature. Some observations that were not understood in the past can now be explained. As an example, the trauma effected with the use of laparoscopic access was more adhesiogenic than that of the same trauma performed with the use of open access, despite the use of a microsurgical approach in both. Now, we have become aware of the damaging effect of the CO₂ pneumoperitoneum [60], whereas in open access the bowels were shielded from oxidative stress caused by the exposure to air by covering the tissues and the use of a silastic membrane. Some tenets of microsurgery should be retested because they are still not clear. These comprise the importance of bowel motility and the use of heparin. In addition, the observation that coating the peritoneal surfaces with HA solution before onset of surgery reduces injury [48] deserves renewed attention. Indeed, this could reduce the effects of exposure of the peritoneal cavity to CO₂ pneumoperitoneum or the oxidative stress of 20% oxygen in air. It likely also decreases tissue manipulation injury.

It is remarkable how easily knowledge of the past is forgotten, especially if not understood well. Obvious reasons are that we rarely go back more than 10 years in searches of the literature, largely because the vast number of articles published makes it prohibitive, and because we think that all important observations will have been picked up in reviews. Moreover, the methods used for the development of microsurgical principles do not comply with our actual understanding of the different levels of evidence. Indeed to make progressive improvements and check the efficacy with the use of a second-look laparoscopy is a highly efficient way to develop the multiple aspects of surgical techniques, although it would often be considered to be observational without evidence. We must also realize that RCTs for each individual aspect of complex procedures are virtually impossible to perform. First, each of the many trials would require prohibitive numbers, because efficacy of each individual small factor would be low. More important is that RCTs and nonhuman animal experiments are not suited for small effects and rare events such as accidents, the prevention of which was the reason for introducing many of our surgical principles. Indeed, to demonstrate prevention of a 1% complication, an RCT of some 6,000 women would be required, using the rule of thumb of 30 “cases” in each arm. Therefore, observational medicine remains the hallmark of surgery in the human. The similarity of conclusions reached during the development of microsurgery in the human and our actual understanding of the role of the peritoneal cavity in animal models emphasizes this. Furthermore, the efficacy of clinical observation is obvious when we realize that today we do not have better answers than 30 years ago for factors such as heparin and bowel motility. A most striking example of this is that only during the discussions to write this Views and Reviews article, one of the authors (P.K.), notwithstanding his interest in microsurgery in the 1970s, fully realized that the improved fertility rates demonstrated for microsurgical principles, can indeed be considered to be the proof of clinical efficacy of what today is called conditioning. In addition, we realized that the adhesiogenic effect of blood in the peritoneal cavity of mice [60] does not take into account the observation of 100 years earlier that blood attaches more firmly to denuded areas.

Experience in microsurgery has enabled the use of a much gentler surgical technique with operative laparoscopy and permitted the recognition that some procedures may still be performed better by modification and improvements of earlier methods. During the years of enthusiastic acceptance of laparoscopic surgery, feasibility of most reproductive and fertility-enhancing procedures by this mode of access was realized. Unfortunately, trials comparing the outcomes of the two approaches were not performed, probably owing to the simple fact that most surgeons may not be equally skilled in both techniques. However, as early as the mid-1980s, it was demonstrated that many complex fertility-enhancing
procedures could be performed by means of minilaparotomy and a microsurgical approach (61, 62). In addition, use of special measures allowed many of these procedures to be done as day surgery, and for the patients to have a postoperative course not dissimilar from those who had a laparoscopic surgery (63, 64). In the absence of comparative evidence and reported successful experience, it may be advisable to approach suitable cases with the use of minilaparotomy, minilaparotomy assisted by laparoscopy, or vice versa, for example, laparoscopic interventions that take a long time and/or are technically difficult, such as a large uterus with large myomas with large defects to suture and specimens to remove.

In conclusion, the principles of microsurgery for adhesion prevention, which were based on available data, intuition, and common sense and confirmed by means of second-look laparoscopy, are still valid today. Experimental confirmation of many of these clinical principles came only recently. It is certainly wise to maintain the tenets of microsurgery, including those for which the efficacy is as yet “not proven” scientifically, until they are proven not to be useful.

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