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Current controversies in tubal disease, endometriosis, and pelvic adhesion

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Reproductive surgery for proximal and distal tubal occlusion, as well as for reversal of tubal ligation, may be an alternative or an adjunct to IVF. Surgery for adenomyosis and endometriosis, including endometriomas, may be considered for the treatment of infertility and/or pelvic pain but carries the risks of surgical complications and diminished ovarian reserve. A greater understanding of the pathogenesis of postoperative peritoneal adhesion formation is needed to develop more effective preventive measures to optimize the clinical results of surgery. (Fertil Steril® 2019;112:417–25. ©2019 by American Society for Reproductive Medicine.)
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While many may feel that reproductive surgery should be abandoned as a primary treatment option for enhancing fertility in favor of IVF, a position we strongly disagree with, it is still necessary as a complimentary treatment for optimizing IVF outcomes for patients with hydrosalpinges and select cases of endometriomas and myomas. This paper will defend the role of reproductive surgery even in the face of ever-improving IVF success rates. Specifically, we will discuss tubal surgery and the surgical management of endometriosis and adenomyosis, as well as the need to reduce postoperative adhesion formation, which may compromise the outcomes of all reproductive surgical procedures.

TUBAL SURGERY

An individualized approach to infertility treatment has been replaced by an "IVF for everything" philosophy. As a result, many reproductive endocrinologists no longer perform reproductive surgery and relegate the treatment of myomas and endometriosis to minimally invasive gynecologic surgeons. However, fertility-enhancing tubal surgery is exclusively the domain of reproductive surgeons with no one to defer to. The following discussion will attempt to make the case against abandoning the surgical management of tubal infertility.

Tubal disease accounts for 25%–35% of infertility, with over half of those cases due to salpingitis. In addition, 10%–25% of tubal infertility occurs at the proximal end (1). Hysterosalpingography (HSG) is the standard test to document tubal patency. However, approximately two thirds of patients with proximal block on HSG are subsequently demonstrated to be patent by repeat HSG or chromotubation at laparoscopy, indicating that the block was due to spasm of the uterotubal ostia or an obstructing plug (2, 3). Hysteroscopic tubal cannulation achieves patency in over 85%, but approximately one third subsequently reocclude. Nearly half of the patients establish an ongoing intrauterine pregnancy (1). A video demonstrating tubal cannulation is available on The Society for Reproductive Surgeons' website (4).

Approximately 25% of women, about 200 million women worldwide, have undergone voluntary sterilization by tubal ligation, with 14% of them regretting their decision. The rate of regret is highest when performed postpartum as well as in younger women (5).

Early attempts at reversal of tubal sterilization with standard macrosurgical techniques were unrewarding. The promotion of microsurgery in the 1970s led to high success rates and remains the gold standard. Initially performed through a full laparotomy incision with an inpatient hospitalization, it is currently accomplished as an outpatient procedure via minilaparotomy. A video demonstrating tubal anastomosis is available on The Society

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for Reproductive Surgeons' website (6). It has also been performed laparoscopically with good success in very skilled hands, although it is technically challenging. Robotic assistance has been incorporated to overcome these difficulties. In fact, the world's first fully robotic surgery was reported in 1999 for reversal of sterilization (7). Retrospective comparisons between minilaparotomy and robotic surgery for tubal anastomosis reported that minilaparotomy was quicker and less expensive and had a higher, although nonstatistically significant, pregnancy rate (8). Furthermore, patients much prefer the cosmetic appearance of a minilaparotomy to the multiple robotic incisions (9).

By whatever means the surgeon elects to accomplish tubal anastomosis, it should be considered the first line of treatment to restore fertility for most cases of tubal sterilization. Pregnancy rates of 70%–90% have been reported for women <40 years of age. Even women >40 have a very respectable 33%–50% pregnancy rate (10–16). A retrospective cohort study that compared tubal anastomosis with IVF concluded that the cumulative delivery rate was significantly higher for anastomosis for women <37 years old but that there was no significant difference in women >37. In addition, the cost per delivery was nearly double that for IVF (17). Decision tree models support that the cost of ongoing pregnancy is only higher for tubal reanastomosis compared with IVF when the woman is > 40 years of age (and increased cost for robotic procedures was even accounted for in one analysis) (18). A third study concluded that tubal anastomosis was more cost-effective even for women >40 (19). The current American Society for Reproductive Medicine committee opinion on the role of tubal surgery concluded that there is good evidence to support the recommendation for microsurgical anastomosis for tubal ligation reversal (20).

In addition to being evidence based, tubal anastomosis is also preferred by many patients who wish to avoid the risk of multiple pregnancy and the inconvenience of the "high-tech" IVF process in favor of a one-time minimally invasive procedure that enables them to attempt to conceive naturally each month. Unfortunately, there are few reproductive endocrinologists who still perform tubal anastomosis. The lack of access to tubal anastomosis is unfortunate not only for our patients today but for future generations of patients as reproductive surgery is no longer an integral part of many fellowship training programs. A survey of reproductive endocrinology fellows reported that 43% of them had not performed a tubal anastomosis as the primary surgeon, a number that has almost certainly increased substantially in the 15 years since this publication (21). It is concerning that tubal anastomosis may no longer be a treatment option for restoring fertility after tubal sterilization. This would certainly be a disservice to our patients.

Another tubal surgical procedure that has all but been abandoned is neosalpingostomy for hydrosalpinges. Two meta-analyses established that the presence of hydrosalpinges reduces IVF implantation, pregnancy, and live birth rates by approximately 50% (22, 23). Salpingectomy and proximal tubal ligation were equally effective in restoring IVF success rates for women without hydrosalpinges (24, 25).

While data on neosalpingostomy are limited, reviewing data from five older noncontrolled studies demonstrated that two-thirds of the patients classified as good prognosis conceived an intrauterine pregnancy, while an ectopic pregnancy occurred in only 3. A video demonstrating neosalpingostomy is available on The Society for Reproductive Surgeons' website (26).

Patients classified as moderate or poor prognosis had poor outcomes and are better served with salpingectomy or proximal ligation followed by IVF (27–31). A more recent prospective study compared pregnancy rates in patient with hydrosalpinges treated by bilateral salpingectomy and IVF versus neosalpingostomy (32). Neosalpingostomy patients who underwent IVF conceived at the same rate as those in the salpingectomy group. Overall, approximately half in each group achieved a pregnancy, but half of the neosalpingostomy patients conceived spontaneously.

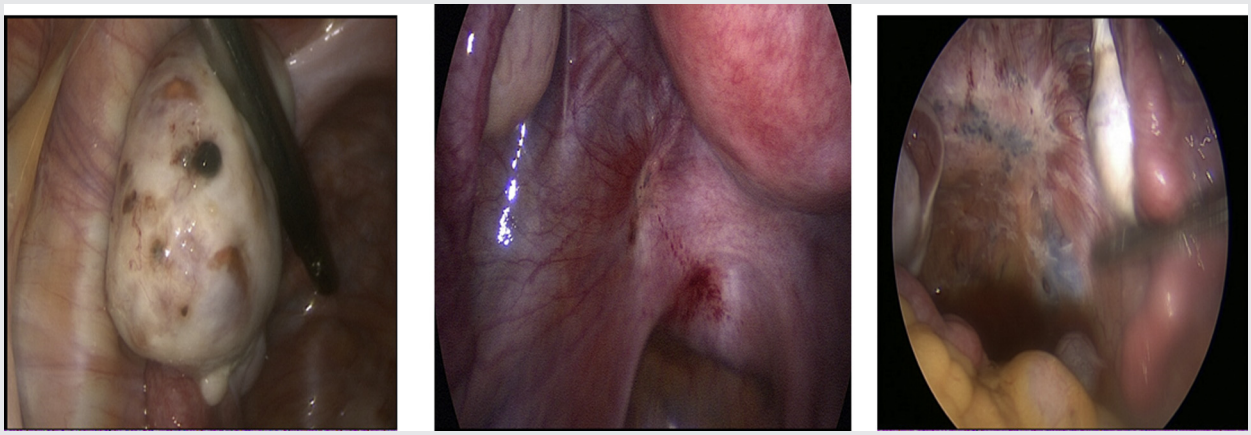
In summary, appropriately selected patients can benefit from a cost-effective, minimally invasive outpatient procedure and avoid the need for IVF. Many patients would prefer this if given the option.

SURGERY FOR ENDOMETRIOSIS AND ADENOMYOSIS

Endometriosis is associated with significant quality-of-life and economic burdens on the patient similar to other chronic diseases such as diabetes (33). Health care costs are mainly due to surgery. There are three overlapping phenotypes that we typically encounter during surgery: peritoneal disease (Fig. 1, superficial ovarian and peritoneal disease), ovarian endometrioma, and deeply infiltrating endometriosis (DIE) (34). In a recent randomized controlled trial in patients with uniquely superficial peritoneal disease, excision and ablation showed similar effectiveness for the treatment of pain (Video 1, available online) (35). As with previous studies, ablation of deep lesions is challenged by the proximity to structures such as the ureter that make excision of lesions a more complete approach.

The management of endometriomas is controversial and has changed with new data on the effect of surgery on ovarian reserve. The diagnosis of an endometrioma can often be made preoperatively due to the classic appearance on ultrasonography of a unilocular cyst, low-level echogenicity of the cyst content, and poor vascularization (36). Endometriomas are typically unilateral and are often associated with more extensive disease. Histologically, endometriomas have a fibrotic capsule, with 60% of the inner wall covered with endometriotic tissue. A critical concept for surgical ablation is that the depth of penetration of this tissue is <1.5 mm (37). Surgical excision of an endometrioma is very effective and is associated with a reduced rate of recurrence, reduced symptom recurrence, and increased spontaneous pregnancy rates (odds ratio, 5.1) compared with ablative surgery (38). However, several studies have shown that excision of an endometrioma is associated with decreased ovarian reserve (39–42). It has been proposed that the intrinsic presence of an endometrioma is associated with decreased ovarian reserve with more impact with bilateral endometriomas (43, 44). Histologic studies have also shown decreased follicular

FIGURE 1



Superficial ovarian and peritoneal disease.

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density in surrounding cortical specimens excised at the time of endometrioma removal (45). One proposed local effect can be attributed to the proinflammatory and oxidative stress observed with an endometrioma.

The observation of postoperative decrease in antimüllerian hormone (AMH) may be due to inadvertent removal of ovarian tissue or destruction of follicles from excessive use of electrosurgery. The amount of tissue removed increases with endometrioma dimension, use of preoperative suppressive therapy, and perhaps surgeon experience (46–48). Longer follow-up studies have been mixed as to whether there is recovery of ovarian reserve as measured by AMH (39). There are techniques that can be used to decrease injury to the ovary such as minimal use of electrosurgery, precise hemostasis, and use of alternative methods to electrosurgery such as hemostatic agents or suture (34). Although alternative techniques to complete excision have been proposed including a combination of excision and ablation, none have been shown to be superior in terms of recurrence rates and ovarian reserve (49). In summary, it appears that surgical intervention is associated with a decline in AMH with risk factors that may amplify this loss such as bilateral endometriomas, low preoperative AMH levels, excision of normal ovarian tissue with the cyst, and excision of recurrent cysts (42, 50).

Recurrence after surgery is approximately 30% within 2–5 years, with ovarian cycle suppression reducing this risk significantly (51–53). Prolonged use of postoperative suppression with oral contraceptives can decrease the recurrence to between 68% and 90%. The use of GnRH agonists did not offer any additional benefit, and they are not recommended as primary agents (54). The levonorgestrol-releasing intrauterine device is inferior to ovarian suppression in preventing recurrence of endometriomas (55).

If the patient is scheduled for IVF there are no data to support that excising or ablating the cyst improves outcome (56). In fact some studies have observed decreased to no ovarian response to controlled ovarian hyperstimulation (57, 58). According to both the American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology, the only indications for pre-IVF surgery are severe pelvic pain and to improve access to follicles (59, 60).

Surgery for DIE is complex and is associated with surgical risk. The deep lesions can be found in many areas such as bladder, ureters, bowel, and rectocervical/rectovaginal tissue planes. In patients with chronic pelvic pain unresponsive to medical management, conservative fertility-preserving surgery is indicated to relieve symptoms (59). Long-term follow-up of patients with advanced disease has shown persistent improvement in quality of life (61, 62). Surgery for DIE requires a detailed knowledge of the retroperitoneal space. Ablation of lesions will not treat these deep lesions, and therefore excision is necessary. Furthermore, these lesions are often near critical retroperitoneal structures such as ureter, bowel, and bladder that can be injured with deep ablation. The critical concept of conservative surgery is postoperative medical suppressive therapy. Generally, suppressive therapy with oral contraceptive agents or progestins is effective. Newer drugs such as elagolix have not been compared with these standard agents or in the setting of long-term suppressive therapy (63). Furthermore, their mechanism of action is to induce a hypogonadal state as with all GnRH agonists or antagonists. Medical treatment does not improve fertility.

In patients with both infertility and pain, a surgical approach can help both aspects. Spontaneous pregnancies are common but highly dependent on how much normal anatomy is restored at the end of surgery. One approach is to use the endometriosis fertility index (EFI), which quantifies the final anatomic structures to predict the probability of pregnancy and whether the patient should still proceed to IVF. For example, in a study where the EFI was extremely low (EFI score, 0–1), the probability of pregnancy was 0%.

If the EFI score was high (EFI, 9–10), the spontaneous pregnancy rate was 46% at 1 year, 58% at 2 years, and 91% at 5 years (64).

Patients with deep lesions involving the bowel with infertility and pain can be treated with a surgical approach that includes rectal shaving (excision of the bowel lesion without entering the lumen), disc excision, and bowel resection. There are opinions published on which approach is best (37). The size of the lesion, depth of penetration that involves the inner muscularis layer, and multifocal nature of the lesion will determine the approach. Although microscopic endometriosis surrounds the macroscopic endometriosis nodules, removal of visible lesions only is associated with excellent outcomes (65). Short- and long-term postoperative complications such as fistula, pelvic abscess, and bowel dysfunction are not uncommon and must be taken into consideration (66, 67).

In a review of spontaneous conception in infertile women on the effect of radical surgery for rectovaginal and rectosigmoid endometriosis, the weighted pregnancy rate in 11 studies was between 25% and 30% (68). In a separate review of the outcome of IVF in women with untreated DIE with bowel involvement, the pregnancy rate was 29% (95% confidence interval [CI], 20%–37%) (69). In general it seems logical to offer IVF to women who are relatively asymptomatic and are infertile, but in women requiring surgery for symptom control, fertility outcomes are comparable. In a comparative study of women with colorectal endometriosis, if surgery preceded IVF, the cumulative live birth rates after three cycles were, for first-line surgery followed by IVF, 32.7%, 58.9%, and 70.6%, and for first-line IVF, 13%, 24.8%, and 54.9% ($P=.0078$) (70). If the patient proceeds to IVF there appears to be no progression of disease or recurrence from the ovarian stimulation (71). The use of the robot for endometriosis surgery does not improve outcomes over conventional laparoscopic surgery (72). There are no published clinical trials that suggest the use of fluorescent dye such as indocyanine green improves outcome, although it may identify occult endometriosis not seen by white light (73).

Adenomyosis is characterized by the presence of endometrial-like glands and stroma within the myometrium. The glandular pockets can be diffuse or localized. The pathophysiology of adenomyosis is unclear, but several theories have been proposed such as invasion of the endometrial basalis layer into the myometrium, metaplasia of pluripotent Müllerian rests, or de novo formation from adult stem cells from the endometrial basalis or bone marrow (74). Historically the diagnosis was only confirmed at histology after hysterectomy. Recently, imaging has been more accurate in detecting the presence of adenomyosis. Prevalence data from these two modalities only reflect its occurrence in symptomatic women. Symptoms associated with adenomyosis include abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, and dyspareunia. Adenomyosis is frequently seen with endometriosis, especially DIE, as well as with fibroids. The relationship with infertility is unclear, although there may be an increase in miscarriage rates after IVF (75). Imaging modalities such as ultrasonography with the three-dimensional mode have demonstrated the characteristic features of enlarged globular uterus, asymmetry of the myometrium, thickened heterogenous myometrium, and myometrial cysts. The accuracy of diagnosis with ultrasound is reported to be 72% (95% CI, 65%–79%) with a specificity of 81% (95% CI, 77%–85 %). Magnetic resonance imaging is reported to have more sensitivity and specificity; these are reported to be 77% (95% CI, 67%–85%) and 89% (95% CI, 67%–85%), respectively (76). Medical management consists of nonsteroidal anti-inflammatory drugs (NSAIDS) and suppressive medical therapy such as oral contraceptives, progestins, levonorgestrol-releasing intrauterine devices, and GnRH agonists. Invariably symptoms recur after discontinuing the medication. Suppressive therapy is recommended after surgical intervention (77). Long-term suppressive therapy with GnRH agonists before IVF has also been shown to improve outcomes (78).

Conservative surgery for the treatment of adenomyosis is indicated in women with severe symptoms unresponsive to medical management who wish to preserve their fertility. It is unclear whether surgical intervention solely to improve fertility is effective. The typical approach to surgical intervention is a wedge resection of an adenomyoma or myometrial thickened area (79). The main concept is that there are no tissue planes and adenomyosis tissue will be left on the sides of the incision. The techniques for hemostasis during adenomyosis resection are similar to those during myomectomy. This surgery can be performed by laparoscopy or by laparotomy. A more radical approach for extensive diffuse adenomyosis is the use of incisions and dissection where serosal and muscular flaps are created with separation and excision of the diseased myometrium with subsequent closure of the serosal and muscular flaps. This surgery can be performed by laparotomy or by minimally invasive techniques depending on the experience of the surgeon. Most of the world literature of over 2,000 surgeries using a more radical approach is from Japan. Surgeons there have reported over 400 pregnancies with 13 cases of uterine rupture (3.6%) (79).

The evolution of the management of endometriosis has been to decrease surgical intervention for both ovarian and nonovarian disease for women with infertility as the sole indication. A decade ago, excision of endometriomas in an infertile patient before IVF was commonplace. Increasingly this is no longer the approach. The evidence is clear that a cystectomy may decrease ovarian reserve. In general, the cyst should be left alone. In patients who have surgery for pain and infertility, the excision of the cyst should be more conservative if the final outcome of the surgery does not establish a normally functioning tube-ovarian anatomy and the patient has a high probability of requiring IVF. In fact, the deeply infiltrating disease under the ovary may be primarily responsible for the pain and should be excised. The cyst should mostly be left alone.

The evolution of the management of deeply infiltrating disease requires experienced surgeons. Many centers now offer a safe surgical approach for excision of this disease, and these centers will continue to expand. There are long-term consequences, but the outcome for management of pain and quality of life is excellent. The controversy about whether we should excise DIE before IVF will continues, but we suspect that a noninterventional approach will be

primarily offered to most patients with infertility as the primary issue.

The surgical approach to adenomyosis is mostly in a state of flux. Few centers offer an integrated surgical approach, and few surgeons have much experience, especially for diffuse adenomyosis. It is not clear which patient would benefit from the surgery. Most importantly, it is not clear what the obstetrical outcome would be when removing a large volume of myometrium. If there were nonsurgical interventions, we predict these would be readily accepted.

ADHESION PREVENTION

Postoperative adhesion formation has been the bane of nearly every surgical specialty. Even in the most skilled hands, pelvic surgery may lead to postoperative peritoneal adhesion formation. These adhesions may result in infertility, pelvic pain, and bowel obstruction as well as increase the risk for intraoperative complications with subsequent surgeries. Thus, it is imperative that effective methods are devised to reduce postoperative adhesions without compromising normal healing. Although there has been no lack of ingenuity during the past century, achieving this goal remains elusive.

Unchanged during the past decade is the clinical recognition of just how often intraperitoneal/pelvic adhesions develop after gynecological surgical procedures. In fact, prior studies demonstrated the high frequency of adhesion development after surgeries performed by laparotomy or laparoscopy (Table 1) (80–93). Also unchanged is the continued belief in the principles of gynecologic microsurgery as the leading approach to limit postoperative adhesion development (94). However, in view of the high frequency with which adhesions develop as just noted, approaches beyond attention to surgical technique are needed.

Efforts to improve the efficacy of reduction or elimination of postoperative adhesion development are dependent on at least a high-level understanding of normal peritoneal healing, as well as what goes awry when adhesions develop (95–97). After surgical tissue injury, there is release of histamine, cytokines, and growth factors, as well as leakage of blood and lymphatic fluid. These biologic changes initiate an inflammatory-like reaction, with recruitment of inflammatory cells and fibroblasts (including myofibroblasts). Simultaneously, the tissue injury results in vascular disruption, diminishing both the delivery of oxygen and nutrients (creating a state of increasing oxidative stress) and removal of metabolic waste products (contributing to a buildup of lactic acid from anaerobic metabolism, with resultant reduction of tissue pH and associated disruption of enzyme function). Additionally, the collection of blood and lymphatic fluid results in development of a serosanguinous mass at the site of tissue injury, the ultimate fate of which is in part determined by the rate of collection and the fibrinolytic potential in fibroblasts and mesothelial cells (which is itself a function of tissue perfusion, with fibrinolytic potential reduced under hypoxic conditions). Of course, modulation of each of these processes occurs and can contribute to ultimate resolution of the fibrosis mass and reperitonealization without adhesion development. Alternatively, if fibrinolysis is impaired, the fibrinous mass persists and fibroblasts that are drawn to the sites of tissue injury invade the fibrinous mass, with subsequent deposition of collagens and other forms of extracellular matrix with reperitonealization over the fibroblast-invaded fibrinous mass and consequent adhesion development. Importantly, after surgical tissue injury, this process is expected to be completed within 3–5 days (unless ongoing tissue injury persists); this thus represents the window of time for approaches to reduce or prevent adhesion development. Of note, if an adhesion has developed, it will "mature" over time with remodeling (with a greater likelihood of becoming dense and opaque) and vascular in-growth. The latter can teleologically be thought of as the body trying to reestablish a supply of oxygen and nutrients to hypoxic tissue, as likely occurs with all healing processes.

Importantly, our understanding of the pathogenesis of pelvic adhesions has expanded upon prior observations of the key role of the extent and degree of tissue injury having a direct correlation with the likelihood of adhesion development (98). The new understanding is that the impact of tissue injury is reflected in the occurrence of oxidative stress, as evidenced by generation of reactive oxygen and reactive nitrogen species (99). A corollary is that adhesion development is likely highly influenced by the metabolic state, with adhesions more likely in the presence of an anaerobic (hypoxic) state (100, 101).

Of note, in addition to these classic factors associated with adhesion development, the potential for the impact of nonclassic factors is becoming increasingly recognized as well (102). Devices currently approved for reduction of postoperative adhesions predate the past decade. The first product to receive FDA approval for reduction of postoperative adhesion was Interceed (80) (oxidized regenerated cellulose, Johnson and Johnson) in 1989. Other products currently approved by the U.S. FDA are Seprafilm (83) (modified hyaluronic acid and carboxymethylcellulose, Genzyme [now Sanofi]) in 1996 and Adept (82) (4% icodextrin solution, Baxter) in 2006. There have been no new adjuvants approved for use in the United States for reduction of postoperative adhesions in the past decade.

There may also be an opportunity to better understand factors important for adhesion development to the uterus in nonpregnant (e.g., myomectomy) and pregnant (e.g., cesarean section) states. Multiple reports have identified that in the absence of an antiadhesion adjuvant after posterior myomectomy, adhesions to the uterus frequently occur in most women in procedures performed at laparotomy (83, 103) and laparoscopy (91, 93). In contrast, uterine adhesion development after an initial cesarean section is considerably less (104) (although repeat cesarean section is associated with dramatic increases in adhesion development). There are multiple potential differences in uterine healing in the pregnant and nonpregnant states that may contribute to these differences in the frequency of adhesion occurrences (105). These include increased uterine blood flow after pregnancy (with potential impact on nutrient and oxygen delivery and metabolic waste removal, influencing the oxidative state), mechanical processes involving the pregnant uterus such as uterine involution; incision

TABLE 1

Adhesion incidence after intra-abdominal use of antiadhesion adjuvants in humans.

Author (ref)	Lap/scope	Site	Treatment control	Adhesion incidence		
				No. of sites	Total sites	%
Azziz (80)	Lap	Pelvic sidewall	Interceed	66	134	49.3
			No treatment	102	134	76.1
Franklin (86)	Lap	Ovary	Interceed	29	55	52.7
			No treatment	41	55	74.5
Nordic (90)	Lap	Adnexae	Interceed	96	198	49.5
			No treatment	140	198	70.7
Sekiba (92)	Lap	Pelvic sidewall	Interceed	23	63	41
			No treatment	48	63	76
Li (87)	Lap	Pelvic adhesions	Interceed	17	27	63
			No treatment	20	27	74
Diamond (84)	Lap	Abdominal pelvic Cavity[a]	Sepracoat (hyaluronic acid)	119	137	86.9
			No treatment	103	108	95.4
Diamond (83)	Lap	Anterior uterus[b]	Seprafilm			61
		Posterior uterus	No treatment			94
			Seprafilm		59	87
			No treatment		68	92
Becker (81)	Lap	Anterior abdominal wall	Seprafilm	42	85	49
			No treatment	85	90	94
Mettler (89)	Combination	Uterus	Spraygel	15	22	68.2
			No treatment	16	18	88.9
DiZerega (85)	Scope	Abdominal pelvic cavity[c]	Adept (icodextrin)	15	22	68.2
			LRS	12	17	70.6
Brown (82)	Scope	Abdominal pelvic cavity[a]	Adept (icodextrin)		203	47
			LRS		199	57
Mais (88)	Scope	Uterus	Hyalobarrier	8	21	38
			No treatment	13	22	41
Pellicano (91)	Scope	Uterus	Hyalobarrier	5	18	27.8
			No treatment	14	18	77.8
Takeuchi (93)	Scope	Uterus	Fibrin gel	10	29	34.5
			Fibrin sheet	20	30	67.7
			No treatment	20	32	62.5

Note: Interceed is oxidized regenerated cellulose; Sepracoat is 4% hyaluronic acid; Seprafilm is modified hyaluronic acid and carboxymethycellulose; Spraygel is polyethylene glycol; Hyalobarrier is crosslinked hyaluronic acid; and Adept is 4% Icodextrin. Lap = laparotomy; scope = laparoscopy; LRS = lactated ringer solution.
[a] De novo adhesion.
[b] With at least one anterior uterine incision.
[c] Reformed adhesions.

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location, which in the pregnant uterus is often the lower uterine segment, which is overlain by the filling and emptying bladder; and the hypercoagulable state in pregnancy. Understanding of the role of these factors in adhesion development may help provide approaches to limit postoperative adhesion development in the future.

The past decade has seen increasing suggestion that alterations to surgical procedures could have a favorable impact on reducing postoperative adhesion development. Foremost has been the concept that performance of procedures by laparoscopy per se, as opposed to laparotomy, will reduce occurrence of adhesions. While this claim predates the past decade, it continues to be difficult to conclusively prove in humans, likely because of the difficulty in testing this hypothesis because of the requirements for designing and conducting conclusive trials. The simple idea that laparoscopy is associated with less tissue drying and less cooling of tissue, and thus results in reduced tissue damage, is confounded by animal studies that demonstrate that laparoscopic insufflation alone can induce adhesion development, in a manner that is dependent on the time, insufflation gas volume, and pressure (106–109). The recent creation of insufflators, which deliver warmed and humidified gas, provide the opportunity to examine the impact on the creation of peritoneal oxidative stress and subsequent adhesion development.

An alternative (although not necessarily mutually exclusive) approach to the prevention of adhesion development between a site of surgery and an adjacent organ is to separate the structures during the healing process, which as noted earlier for the peritoneum, is thought to take no more than 3–5 days. Instead of using a barrier on the injured surface (or in addition to the use of a barrier), there is the option to mechanically hold a structure away from the healing surface. A specific situation where this approach has been used is temporary ovarian suspension, to keep the ovary separate from the pelvic sidewall and other pelvic structures. Descriptive studies suggest this may be of benefit (110), although well-designed studies to more definitively assess the value of temporary ovarian suspension are needed.

In summary, prevention of postoperative development is likely one of the greatest unmet needs in surgery today. While the past decade has solidified our understanding of factors important to the pathogenesis of adhesion development, and new molecular biologic and clinical observations have

added to this understanding, there remains a major unmet need to fully understand adhesion pathogenesis. A major challenge that has limited progress to date is the biologic similarity between "desired" healing, such as closure of the abdominal wall, the peritoneum, and organs (such as the uterus after myomectomy and the ovary after cystectomy), and adhesions development. Identification of differences in the molecular process involved, between desired healing and adhesion development, will likely be key to the initiation of targeted therapies to prevent development of adhesions.

Lastly, a challenge in the past decade has been the widespread recognition not only by the public, but also by surgeons, hospital officials, and insurance administrators, of the high frequency of postoperative adhesions development and the devastating morbidity they can cause years or decades later. Recognition of these basic facts will undoubtedly result in greater use of antiadhesion adjuvants, as well as other approaches to reduce postoperative adhesions. However, the current health care policies/systems in the United States also may be a factor in the low use of these products, as officials/administrators may be responding more to current expenses as opposed to health outcomes years later, when care providers, location of care, and health insurance may differ from those at the time of the surgical procedure. Although the last decade has not yielded definitive long-term economic assessments, there have been attempts at economic modeling that do demonstrate a societal economic benefit to the use of antiadhesion adjuvants (111, 112).

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