

Infertility treatment: the viability of the laparoscopic view

Assisted reproductive technology (ART) and laparoscopy are not mutually exclusive, but coexisting and potentially complimentary treatments. For disease conditions contributing to infertility in addition to other concomitant or potential morbidity, laparoscopy represents a more comprehensive approach. (Fertil Steril® 2008; 89:461-4. ©2008 by American Society for Reproductive Medicine.)

More than a decade ago, Dr. Alan DeCherney wrote "the obituary of laparotomy for pelvic reconstructive surgery has been written; it is only its publication that remains" (1). These sentiments issued in 1985 appear prophetic today, as laparoscopy has largely supplanted laparotomy in the treatment of most gynecologic pathology. Whether assisted reproductive technologies (ART) will render laparoscopy a similar fate in the context of fertility treatment is the subject of the current debate. Clearly, IVF represents a popular and effective option for many couples with infertility. Yet, our position is that a role for laparoscopy in the optimization of fertility will continue. This position is based on several arguments. First, concerns exist regarding ART outcomes, and women affected by conditions amenable to laparoscopic treatment may welcome an alternative approach that obviates IVF. Second, for disease conditions that cause infertility in association with other morbidity, laparoscopic treatment results in a more holistic approach to the patient. In particular, laparoscopy represents an alternative to IVF for women affected with fibroids or endometriosis, and an adjunct for improving IVF treatment success in women with hydrosalpinges.

By current estimates, 1% of infants born in the United States are conceived by ART. Increasingly, however, studies are highlighting concerns with ART outcomes. Several investigators have reported increased complications associated with ART conceptions, to include an odds ratio (OR) of 2.2 for congenital anomaly (2) and an OR of 1.6 for intrauterine growth restriction (3). In addition, a recent meta-analysis revealed an increased risk of preterm delivery (OR 1.95) and perinatal mortality (OR 2.19) in singleton gestations conceived by ART (3). These obstetric and neonatal risks are even greater for multiple gestations, an occurrence reaching epidemic proportion in the setting of ART. Of more than 31,000 pregnancies reported in the 2003 Society of Assisted Reproductive Technology (SART) data-

base, 29% were twin gestations and 5.9% were higher order multiple gestations. The economic and social costs associated with multiple births are well documented. Although strategies to reduce the high prevalence of multiple gestation, such as better embryo selection protocols and single embryo transfer exist, payership dynamics associated with IVF in the United States render multiple embryo transfer common. Finally, the practice of IVF entails the use of gonadotropin preparations for supraphysiologic follicular recruitment. Ovarian hyperstimulation syndrome (OHSS) is a common complication of ovulation induction. Although the prevalence of severe OHSS is low, it is nonetheless an iatrogenic complication of a nonvital treatment. The long-term effect of controlled ovarian hyperstimulation (COH) in terms of ovarian cancer risk is unknown. Currently, epidemiologic data do not show a conclusive association between invasive ovarian cancer risk and gonadotropin use, although an increased risk of borderline ovarian tumor development has been reported (4). Whether this increase in risk is consequent to the treatment or to the underlying condition that required the treatment is uncertain.

Given these concerns, alternatives for the optimization of fertility, where appropriate, deserve consideration. Surgery has demonstrated benefit in the management of a variety of conditions associated with infertility. Laparoscopy has effectively replaced laparotomy in the management of these conditions. This was true as early as 1985 when Dr. DeCherney wrote, "It is apparent that little remains in the reproductive surgeon's armamentarium that can't be accomplished through the use of a laparoscope" (1). Since then, numerous studies and meta-analyses support the benefits of laparoscopy in terms of improved cosmesis, less postoperative pain, shorter hospital stay, decreased cost, decreased febrile morbidity, and lower incidence of de novo adhesion formation (5-8).

A role for laparoscopy is well supported in the treatment of hydrosalpinx-associated subfertility. Hydrosalpinx entails an accumulation of fluid in the fallopian tube subsequent to distal tubal blockage. This embryotoxic fluid then seeps proximally into the endometrial cavity where it has deleterious effects on embryo survival and implantation. Clinically, the presence of a hydrosalpinx has negative

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consequences in terms of implantation, pregnancy (PR), and delivery rates. The observed reduction in PRs is not ameliorated by IVF. At least eight separate studies demonstrate a decline in IVF PRs in the presence of a hydrosalpinx with a consistent 50% reduction in these studies (9). A meta-analysis comparing 1,144 IVF cycles with hydrosalpinx with 5,569 control cycles demonstrated a 50% reduction in implantation rates and PRs and a twofold increase in the miscarriage rate (10). Based on evidence accumulated from three separate randomized controlled trials, salpingectomy is effective in improving the odds of achieving pregnancy. A pooled analysis of these studies showed that salpingectomy for hydrosalpinx resulted in a 1.75-fold and a 2.13-fold higher odds of pregnancy and live birth, respectively (11). Importantly, this meta-analysis showed a statistically significant benefit of laparoscopic salpingectomy for hydrosalpinges before IVF. Treatment with salpingectomy does not appear to negatively affect ovarian responsiveness to gonadotropin treatment (12). Alternatives to laparoscopy in the management of hydrosalpinx are few. Retrospectively, studies investigating transvaginal needle aspiration report conflicting results (13–15) and this technique is associated with rapid reaccumulation of hydrosalpingeal (16) and endometrial (17) fluid. The accumulated clinical evidence led the ASRM Clinical Practice Committee to conclude, "Salpingectomy performed for hydrosalpinx prior to IVF improves subsequent pregnancy, implantation and live birth rates" (18). In sum, consensus exists regarding a role for laparoscopy in the management of hydrosalpinx-associated subfertility.

Laparoscopy appears to show benefit in the management of appropriately selected patients with uterine fibroids and infertility. Uterine fibroids are detected in 5%–10% of women undergoing treatment for infertility and are identified as the sole factor in up to 2.4% of infertile women (19, 20). These lesions may affect fertility by both mechanical and biochemical mechanisms (21, 22), and have been associated with fetal wastage and premature delivery. The impact of fibroid removal versus no removal on subsequent fertility treatment outcomes has yet to be evaluated in an appropriately designed prospective randomized trial (23). Nonetheless, it is well recognized that removal of submucosal fibroids is associated with improved PRs (24), and that hysteroscopy represents an ideal approach. However, in many cases, the submucosal aspect of the fibroid is analogous to the "tip of the iceberg," and hysteroscopic myomectomy alone may result in recurrence of the lesion. In these cases, the myomectomy must include a peritoneal approach to afford complete resection of the lesion. More controversial is the impact of intramural or subserosal fibroids on fertility. Several meta-analyses of retrospective studies established that intramural fibroids, which distort the endometrial cavity decrease fertility, and that removal of these lesions increases fertility by an amount equal to that of infertile controls without myomas (20, 24). Yet, retrospective studies have demonstrated reduced IVF PRs in women with

intramural fibroids that do not distort the cavity, and this association was particularly robust for large (>4 cm) fibroids (25–27). More recently, a retrospective review of IVF outcomes in women with small (≤ 5 cm) fibroids compared to women without fibroids showed a 45% reduction in the live birth rate (hazard ratio [HR] = 0.55, 95% confidence interval [CI] = 0.32–0.95, $P=.03$) after adjusting for confounders (28). Laparoscopy and laparotomy in the approach to myomectomy have been compared in a prospective randomized trial (29). This study found no difference in fertility or obstetric outcomes between these two approaches, but noted significant advantages to laparoscopy in terms of blood loss, operative time, and inpatient stay. Alternatives to surgery include magnetic resonance imaging (MRI)-guided focused ultrasound surgery and uterine artery embolization. Very limited data exist regarding fertility and pregnancy outcomes after MRI-guided focused ultrasound surgery (30). Compared to laparoscopic myomectomy, uterine artery embolization was associated with an increased risk of preterm delivery (31). In summary, the available evidence suggests an important role for pre-ART laparoscopic myomectomy in the management of fibroid associated infertility.

Endometriosis represents another condition for which laparoscopy has a viable role in the optimization of PRs. The association of endometriosis with infertility is well documented. Although heterogeneity of endometriosis prevalence estimates is recognized, the pooled estimates suggest that infertile women are five times more likely to be affected by endometriosis than fertile women (32). A meta-analysis of 22 published studies demonstrated a nearly 50% reduction in IVF pregnancy outcomes in women with endometriosis compared to women with tubal factor infertility (33). The negative association of endometriosis with IVF PRs was especially pronounced in more advanced stages of disease. Significantly, this meta-analysis provided some insight as to the mechanisms by which endometriosis may affect fertility. The presence of endometriosis was found to affect multiple parameters to include ovarian response, oocyte quality, embryo quality, and implantation. An oocyte sharing study demonstrated that oocytes from women with endometriosis had a statistically significant decrease in PR regardless of the endometriosis status of the recipients, implicating abnormal oocyte development in endometriosis-associated infertility (34). These deleterious effects on fertility may be secondary to the inflammatory milieu that occurs with this condition (35). A retrospective study showed no difference in 3-year cumulative PRs between women with endometriosis who underwent laparoscopic treatment followed by IVF and women with endometriosis who underwent laparoscopic treatment alone (36). Several randomized controlled trials have been conducted to prospectively evaluate the role of laparoscopic treatment of infertility in women with endometriosis (37, 38). A meta-analysis of these two studies showed a statistically significant increase in the combined live birth/ongoing

PR with laparoscopic treatment of minimal–mild disease versus laparoscopic diagnosis only (39). Although a similar study in more advanced stages of endometriosis has not been published, uncontrolled trials show increased PRs for women with moderate–severe disease if normal tubo-ovarian relationships are restored (40, 41). A randomized controlled trial comparing the interventions of laparoscopic surgery versus IVF for the treatment of endometriosis-associated infertility has not been published.

Thus far we have considered the evidence for treating pelvic pathologies as they relate to infertility alone. However, these pathologies are responsible for other patient complaints or conditions in addition to infertility, which make laparoscopy especially favorable. For example, menorrhagia associated with fibroids can result in significant anemia that, left untreated, may compromise both fertility and obstetric outcomes. Likewise, endometriosis-related pain may flare considerably in the setting of hyperestrogenemia associated with gonadotropin-based ovarian stimulation, and this can significantly compromise treatment (42). Endometriosis is associated with anatomic distortion that can progress to the point of organ dysfunction or compromise, as exemplified by cases of asymptomatic renal failure secondary to ureteral endometriosis (43). Recent studies point to an increased risk of ovarian cancer in the setting of endometriosis (44), and future studies may support heightened surveillance based on the detection of endometriosis. For situations such as these the benefits of laparoscopy extend beyond the concomitant optimization of fertility.

Given the increased availability and affordability of IVF, laparoscopy is often bypassed, even in patients with known or suspected pelvic pathology. This move from a “diagnostic” to a “prognosis” oriented approach to infertility care is not necessarily clinically or cost effective. In a group of patients who failed to achieve pregnancy after ovulation induction with clomiphene (CC), the finding of (treatable) pelvic pathology was substantial, with the prevalence of stage III–IV endometriosis, pelvic adhesions, or tubal disease reaching 35% (45). Patients with endometriosis who undergo a cycle or more of IVF without success despite good ovarian response and quality embryos should be considered for laparoscopic management. The benefit of this approach for patients with endometriosis was recently demonstrated. In a series of 29 women who had failed an average of two IVF cycles previously, laparoscopic treatment of endometriosis resulted in successful pregnancy in 22 patients (46). Of note, many (15/29) of the women who successfully conceived did so without further IVF, including 13 spontaneous pregnancies. In addition, the benefit was observed irrespective of the stage of disease at laparoscopy, with more than 60% (8/13) of patients with stage IV endometriosis achieving pregnancy. Compared to a cohort with a similar mean age and mean number of failed cycles who did not undergo laparoscopy, a significant improve-

ment in PR ($P < .01$) was observed in the laparoscopic treatment group. These observations suggest that, even in the setting of multiple IVF failures, laparoscopic management of endometriosis remains a successful treatment option for infertility.

The goal of infertility treatment is the attainment of a healthy pregnancy. Clearly ART offers great promise in achieving this goal. Yet the concerns of multiple birth and obstetric outcomes should be weighed in choosing this course. Laparoscopy provides a mechanism to diagnose and treat underlying pelvic pathology that may be causative for infertility as well as other symptoms, thereby optimizing both spontaneous and assisted PRs. Assisted reproductive technology and laparoscopy are not mutually exclusive, but coexisting and potentially complimentary treatments. The choice of approach is an individual one, made in the context of the complexity of medical, social, and financial variables that are unique to each couple. With proper patient selection, laparoscopy represents an effective option for optimizing pregnancy potential that we anticipate will retain its viability well into the future.

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