Competing Endoscopic Surgeries in the Era of Assisted Reproductive Technologies: Evidence and Practice

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ABSTRACT

Now-a-days the assisted reproductive technologies (ART) are progressing and advancing rapidly. Many reproductive medicine specialists do believe in ART to be the first choice for infertile women regardless of age related issues while gynecologists do believe in reproductive surgery as basic treatment option for these patients. Debate is still unsolved between reproductive surgery or ART which is the first choice for management of infertility. Many issues increase the complexity of the debate as age of infertile patient, ovarian reserve and previous management whether surgery or ART. In this review, both aspects were discussed to clear some aspects of this debate. The objective of this review is to highlight this debate and mention the aspects which help gynecologists and reproductive surgeons to choose the best for infertile patients.

KEY WORDS: Endoscopic reproductive surgeries; Assisted reproductive technologies; In Vitro fertilisation/Intracytoplasmic sperm injection (IVF/ICSI).

ABBREVIATIONS: ART: Assisted Reproductive Technologies; IVF: In Vitro Fertilisation; ICSI: Intracytoplasmic sperm injection; LOD: Laparoscopic Ovarian Drilling; CPR: Cumulative Pregnancy Rates; PCOS: Polycystic Ovary Syndrome.

INTRODUCTION

The role of endoscopic surgeries prior to assisted reproductive technologies (ART) is a matter of debate where some studies stress on its importance, other studies confirm its importance only in selected cases, and other studies minimize its role before in vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) procedures.1,2

Now-a-days IVF/ICSI procedures are widely spread worldwide and are replacing reproductive surgical procedures limiting its role as first-line treatment. This change in clinical practice may be due to the higher cost-effectiveness of IVF/ICSI compared to reproductive surgery or may be preferred due to other factors such as a lack of surgical expertise, patient’s desires to achieve rapid results or the fear of procedure-related complications.3

ENDOSCOPIC TUBAL SURGERY

Tubal surgery is the first-line management option for young women less than 35-years-old with minor tubal pathology. The second option should be IVF if there are other factors affecting fertility, if the patient is >38-years-old, if patient had moderate to severe tubal disease, and if one year or more had passed post-surgery for tubal pathology.4

Salpingectomy and ART

Hydrosalpinx is a common tubal pathology that affects IVF/ICSI results by many mechanisms. Surgical treatment should be considered for all women with hydrosalpinges prior to IVF/ICSI procedures. Previous evidence supported only unilateral salpingectomy for a unilateral hydro-
salpinx (bilateral salpingectomy for bilateral hydrosalpinges). Now evidence supports laparoscopic tubal occlusion as an alternative to laparoscopic salpingectomy in improving pregnancy rates in women with hydrosalpinges.5

Further studies are required to assess the value of aspiration of hydrosalpinges prior to or during IVF/ICSI procedures and also the value of tubal plastic surgery as an alternative (or as a preliminary) to IVF.5

Other studies were not advocating salpingectomy prior IVF/ICSI due to its deleterious effects on ovarian reserve. Available data suggested an absence of variation in ovarian reserve markers after unilateral salpingectomy while contradictory results were reported for bilateral surgery. Evidence supports unilateral salpingectomy and considers it a safe procedure, without negative effects on ovarian reserve and ovarian response to gonadotropins stimulation; moreover, it has a positive effect on pregnancy rate. Benefits of bilateral salpingectomy before IVF/ICSI and its safety on ovarian reserve, needed to be confirmed by further trials as the available studies regarding this issue are conflicting.6

Tubal Cannulation and ART

Tubal block is another tubal pathology where some studies advocate laparoscopic salpingectomy prior IVF/ICSI procedures as it has a significant improvement in ongoing pregnancy/live-birth rate without significant reduction in ovarian response to gonadotropin stimulation.7

Honoré et al8 in a meta-analysis examined the value of tubal microsurgery and macrosurgery, and hysteroscopic management of proximal tubal occlusion. They found that the average pregnancy rate was higher in women managed by hysteroscopic tubal recanalization compared with those managed with tubal microsurgery and open surgery or selective salpingography (48.9% vs. 38% vs. 28.8%, respectively).

A more recent review evaluated success and pregnancy rates of tubal recanalization with hysteroscopy where the success rates ranged from 57% to 88% with partially occluded tubes or with complete occlusion in the cornual, proximal, and intrauterine/interstitial portions of the fallopian tube. One study that was reviewed reported a success rate of 13.3% for distal tubal occlusion after hysteroscopic tubal cannulation.8

Tubal Sterilization Reversal and ART

Laparoscopic tubal reversal is a difficult operation, time consuming and success rates are comparable to IVF/ICSI procedures allowing many gynecologists to choose ART over laparoscopic reversal of tubal sterilization.10,11

Considering number of desired children, cost/benefit ratio and age of patient may change the choice between the 2 treatment options for laparoscopic tubal reversal over ART especially if patient is young and wishing more children. If only one more child is desired and the woman is older than 35 years of age, perhaps IVF is the best choice.10,11

Beyond age 40, the success with either tubal reversal or IVF is extremely low less than 1-3% in most reports. In this situation cost/benefit ratio should be considered and tubal reversal becomes the more cost-effective option.12

In a Belgian retrospective study published in 2007, the difference in pregnancy rates between IVF and tubal reversal were statistically insignificant until they were examined by age of the woman. It became clear that cumulative pregnancy rates for women under 37 were significantly better for tubal reversal; for women over age 37 the rates were better for IVF. However, for all age groups in all published reports the success-per-cycle rates in IVF are better than those for tubal reversal.13

The decision between IVF and tubal reversal is highly complex and profoundly affected by the factors of age, cost and time as well as the presence of other potential infertility problems. Each couple facing this decision must be assessed and counseled individually to ensure selection of the treatment option best suited to them.10-13

ENDOSCOPIC UTERINE SURGERY

Although, a great progress in ART occurs every day, there are still unknown factors limiting successful implantation and decreasing percentage of both clinical and ongoing pregnancy rates. These facts suggest an underestimated role for the uterus in the success rates of ART.14

Some studies advocated and recommended the use of office hysteroscopy as a routine procedure in the infertility work-up.15-19 It has become easy to perform in an outpatient setting without anesthesia. Moreover, it offers direct visualization and enables clinicians to diagnose and treat intrauterine pathology during the same session.20,21

One study found a significant concordance between 3D transvaginal ultrasound and hysteroscopy (RR 0.77, 95% CI 0.6-0.84). The authors advocated 3D ultrasound imaging of uterine cavity prior to IVF/ICSI even in women recurrent implantation failure and considered 3D a sufficient tool for evaluation of the endometrial cavity before IVF. That study stated that any problems missed by conventional transvaginal ultrasound are not relevant to the outcomes of IVF.22

Recent studies, address the importance of the morphological evaluation of the uterus through assessment of the effect of office hysteroscopy on IVF outcomes in women undergoing IVF for the first time and in women with recurrent implantation failure.23-25

The results of these studies suggest that there is no reason to perform hysteroscopy before IVF, irrespective of whether...
the woman is about to undergo the first cycle of IVF or if she has undergone several failed IVF attempts, as long as conventional transvaginal ultrasound shows no uterine pathology. These studies did not find an answer on the significance of hysteroscopic correction of the common intrauterine lesions as polyps, submucous myomata or partial septae prior to IVF/ICSI and their relation to pregnancy rates.23-25

**ENDOMETRIAL TRAUMA PRIOR INTRACYTOPLASMIC IN VITRO FERTILISATION/SPERM INJECTION (IVF/ICSI)**

From practical point of view, many gynecologists and reproductive medicine specialists trust in diagnostic plus traumatic effects of hysteroscopy prior IVF/ICSI cycles. On the other hand evidence proved that hysteroscopy does not seem to improve implantation through a hypothetical pro-inflammatory effect.26

**Hysteroscopy after Repeated IVF Failures**

Hysteroscopy increases pregnancy rates even in the absence of intrauterine pathology in women with recurrent IVF failure. This could be explained by the cervical dilatation and/or direct hysteroscopic visualisation of the uterine cavity facilitating embryo transfer or alternatively by an immunological mechanism triggered by the hysteroscopic manipulation or by the effect of the distension medium on the endometrium.26

**Uterine Fibroids and ART**

Submucosal fibroids negatively affect fertility, especially fibroids larger than 4 cm, even without cavity distortion. Fibroids impair fertility by many mechanisms involving alteration of local anatomical location, inducing functional changes of the myometrium and endometrium, and finally endocrine and paracrine molecular mechanisms which could alone or in combination cause reduced reproductive potential, impaired gamete transport, diminished implantation, and creation of a hostile environment.27

Hysteroscopic excision of submucosal myomas seems to restore fertility with pregnancy rates after surgery similar to normal controls. Even open excision of intramural myomas seems to be associated with higher pregnancy rates when compared to non-operated controls, although evidence is still not sufficient. The results of endoscopic and open myomectomy are similar, thus, endoscopic treatment is the recommended approach due to its advantages in patient’s post-operative course.28

Casini et al29 analyzed whether the removal of fibroids before conception improves pregnancy rates and outcomes compared with no surgery. In that study 92 patients underwent myomectomy, via either hysteroscopy or laparotomy, and 89 patients did not undergo surgery. All patients were followed-up for 12 months to determine the rate of clinical pregnancy. Higher pregnancy rates were observed in the patients who underwent myomectomy with submucous fibroids (43.35% vs. 27.2% in the non-surgical group) or submucous and intramural fibroids (36.4% vs. 15% in the non-surgical group) (p<0.05). There was no statistically significant increase in pregnancy rate in the patients with only intramural or intramural and subserosal fibroids (p>0.05).

Pritts et al30 in a meta-analysis of 23 studies evaluating women with fibroids and infertility. The authors found that a large difference between infertile women with submucous fibroids and those without submucous fibroids as regard pregnancy rate, implantation, and ongoing pregnancy/live birth rates, as well as the spontaneous abortion rate. They found also that women who underwent a hysteroscopic myomectomy had greater clinical pregnancy rate compared with those with fibroids left in situ.30

Cochrane database found that in a subset of women with a submucous fibroid (n=94), there was a statistically insignificant increased odds of clinical pregnancy (odds ratio, 2.4; 95% confidence interval, 0.97-6.2; p=0.06).31 Shokeir et al32 found similar results in their randomized controlled study.

**Uterine Septum Surgery and ART**

The debate for infertile women with uterine disease, such as myoma and adenomyosis, is whether infertility treatment including ART should be the first choice considering the aging of eggs, or whether surgery for uterine disease (as the cause of infertility) should precede ART.33

Abnormal uterine anatomy and function are major factors affecting success of fertility treatments. Uterine pathologies, including congenital or acquired lesions, have been reported in 21-47% of patients undergoing in vitro fertilization cycles. In another study these abnormalities were found to be lower than reported representing only 11%.34,35

Some studies answered the question that hysteroscopy could enhance fertility in cavity uterine lesions or not where they found that hysteroscopic surgery enhanced fertility in most of the congenital and acquired problems affecting women and concluded that both diagnostic and operative hysteroscopy are rapid and safe procedures to improve fertility.34,36

Uterine septum is not only associated with infertility but also is associated with increase rates of pregnancy loss as high as 90%. The American Fertility Association (AFA), now known as the American Society of Reproductive Medicine (ASRM), explained these septum related pregnancy wastages by structural alterations in the endometrium of the septum, which affects implantation.37

Mollo et al38 studied 2 groups with unexplained fertility, a group of women with septate uterus who underwent hysteroscopic metroplasty and a control group without septate uteri. The 2 groups were similar in terms of age, duration of infertility, and body mass index (BMI). The pregnancy rate and live birth rate were significantly higher in the hysteroscopic metroplasty group.
compared with the control group (38.6% vs. 20.4%; p=0.016 and 34.1% vs. 18.9%; p<0.05, respectively).

Pabuçcu and Gomel evaluated women aged 21-35 years with unexplained primary fertility and septate uteri who underwent hysteroscopic metroplasty. Five women (8.2%) underwent repeat surgery for a residual septum >1 cm. The outcome of that study was a 41% pregnancy rate, with a 29.5% live birth rate. In 13 of the 18 pregnancies that carried to term, 2 patients had a total septum and 11 had a subtotal septum resected.

Although, hysteroscopic metroplasty appears to improve fertility, the role of surgical correction in patients with primary infertility remains under debate. An older prospective study identified a reduction in pregnancy wastage from 87.5-44.4% and recommended hysteroscopic metroplasty as the treatment of choice in patients experiencing recurrent abortions.39,40

Looking further at septum length, Shokeir et al studied women with septum length of ≥2.5 cm and compared them with women with a septum length of <2.5 cm. All of the 42 women (47.7%) who achieved pregnancy were age <40 years with <3 years of infertility; 8% of these pregnancies were spontaneous. The pregnancy rate was 66.7% in those with a septum length of ≥2.5 cm and 42.8% in those with a septum length of <2.5 cm. The overall live birth rate was 40.1%.41

Grimbizis et al reviewed 6 studies published before 2001 that reported a live birth rate of 6.1% in women with intact septums compared with 82% in those women who underwent hysteroscopic metroplasty. Nouri et al performed a more recent literature search that revealed live birth rates ranging from 26% to 73%, with a cumulative rate of 45%, after hysteroscopic metroplasty. Both of these reviews evaluated studies in women with a septate uterus, and both unexplained primary infertility and recurrent abortions.

More recently Abuzeid et al conducted a historical cohort study, to determine reproductive outcome after (IVF/ICSI) in women with primary infertility following hysteroscopic septoplasty of incomplete uterine septum or arcuate uterine anomaly. They found that there was no significant difference between the hysteroscopic septoplasty and control groups in the clinical pregnancy (74.4% vs. 67.3%) or in the delivery (65.4% vs. 60.2%) rates per patient, respectively. They concluded that reproductive outcome of in vitro fertilization pre-embryo transfer (IVF-ET) after hysteroscopic correction of incomplete uterine septum/arcuate uterine anomaly in women with primary infertility is no different from women with normal uterine cavity.

Uterine Polyp Excision and ART

Uterine polyps can cause infertility by many mechanisms which include irregular endometrial bleeding, inflammatory endometrial response, obstructive inhibition of sperm transport, physical obstruction of exposure of the embryo to the endometrium, interference with normal patterns of endocrine function, and inhibition of sperm binding to the zona pellucida.45

In 2005, Pérez-Medina et al evaluated 204 women with infertility for 2 years or more. The study group (n=101) underwent hysteroscopic polypectomy, whereas the control group (n=103) underwent hysteroscopic polyp biopsy only. After either procedure, participants were to receive up to 4 intrauterine insemination cycles. They concluded that, there were no significant differences between groups in polyp size and pregnancy conception rates (p=0.32).46

Stamatellos et al in a retrospective study evaluated the impact of the size and number of uterine polyps on fertility in women with primary or secondary infertility for more than one year. The participants were divided into 2 groups, those with a polyp ≤1 cm and those with a polyp >1 cm or multiple polyps. The pregnancy rate was 61.4% for the entire study population undergoing hysteroscopic polypectomy, irrespective of whether the patient had primary or secondary infertility. The findings of that study correlated with those of Pérez-Medina et al, with polyp size and number of polyps having no significant association with pregnancy rate.

Another retrospective study conducted by Yahaihara on 230 women to determine the significance of the location of endometrial polyps. The locations were defined as anterior wall, posterior wall, lateral wall, utero-tubal junction, and multiple polyps. Similar to previously reported findings, polyp size in any area of the uterus did not significantly impact pregnancy rate; however, the highest pregnancy rate, 50-60%, was achieved in those who had polyps removed from the utero-tubal junction. Similar results were obtained by Ghaffari et al who reported no significant difference in pregnancy rates by polyp location.

Asherman’s Syndrome and ART

Intrauterine adhesions are not life threatening, and may be asymptomatic in many patients. The main symptoms of Asherman’s syndrome include pain, infertility, and abnormal menstrual patterns especially amenorrhea and scanty menstruation.50

Hysteroscopy has been the method of choice in the investigation and treatment of the condition. Management of moderate to severe disease may be a challenge, and repeated surgery may be necessary in some cases and may not always produce the desired outcome.51,52

A prospective study evaluated 24 women with infertility (12 of whom had previously delivered) and 12 women with a history of recurrent abortions. Of these 24 women, 48% conceived after hysteroscopic adhesiolysis. Among the 12 women with recurrent abortions, pregnancy wastage was reduced from 86.5-42.8% post-operatively.53

Another study, conducted by Tsui et al conducted a study on 4 cases of severe Asherman’s syndrome where hysteroscopic adhesiolysis was done for all cases. They found that all
the women (100%, 4/4) conceived successfully (three undergoing IVF & ET, and one had a spontaneous pregnancy). They concluded that hysteroscopic adhesiolysis has promising reproductive outcomes for infertile women with severe Asherman syndrome.

A more recent study enrolled 357 patients with mild, moderate, and severe Asherman’s syndrome who underwent hysteroscopic adhesiolysis between January 2012 and December 2015. They found that the reproductive outcomes of 332 women (93%) were followed for an average duration of 27±9 months, and the overall conception rate after hysteroscopic adhesiolysis was 48.2%, which decreased with increased intrauterine adhesions (IUA) severity (mild, 60.7%; moderate, 53.4%; severe, 25%). The mean time to conception following hysteroscopic adhesiolysis was 9.7±3.7 months. The miscarriage rate was 9.4%, and the live birth rate was no lower than 85.6%. Eleven patients (7.9%) had postpartum hemorrhage, including 6 (4.3%) due to adherent placenta and 3 (2.1%) due to placenta accreta.55

ENDOSCOPIC OVARIAN SURGERY AND ART

Benign Ovarian Cysts and Endometriomas

The debate here remain unsolved as many gynecologic surgeons believe in the role of laparoscopic cystectomy for treatment of benign ovarian cysts, other reproductive medicine specialists antagonize this treatment option as it may influence women’s fertility. There are no randomized trials comparing laparoscopic excision to expectant management before IVF–ICSI cycles. The idea that surgery increases IVF pregnancy rates is not supported by the available evidence.56

A review study was conducted by Legendre et al57 to explore the potential relationship between ovarian cysts, their treatment, and infertility. They concluded that surgery does not seem to improve pregnancy rates. The best surgical approach is the laparoscopic approach. The surgical options studied were excision, sclerotherapy and plasma vaporization which were found to be promising, offering a greater preservation of the ovarian parenchyma, especially in endometriomas.

Kostrzewa et al58 conducted a study to compare women’s fertility after laparoscopic cystectomy of endometrioma versus other benign ovarian tumors. They found that there is a low pregnancy rate after laparoscopic cystectomy of benign ovarian tumors. Moreover, pregnancy rate after cystectomy of endometrioma is significantly lower and the percentage of recurrence of endometrioma is significantly higher. They concluded that the decision about surgical treatment among childbearing women must be well-considered because of the risk of subsequent surgery in the future.

Shervin et al59 conducted a similar study to evaluate the result of laparoscopic endometrioma excision in fertility outcome of advanced endometriosis patients. They found that cumulative pregnancy rates (CPR) did not show any statistical significance between cases (35.6%) and controls (39.5%) (p value=0.959). The regression analysis of covariates showed there is no significant relationship between cystectomy and fertility outcome. They concluded that fine excision and stripping of the endometrioma along with radical resection of deep lesions improves fertility without any significant adverse effect in comparison with patients with intact ovaries.

Studies recruiting women with unilateral endometrioma and comparing ovarian responsiveness in the affected and contralateral intact ovary indicate that excision of endometriomas is associated with a quantitative damage to ovarian reserve. Other issues linked to laparoscopic surgery for endometriomas include costs and hazard of surgical complications. All above-mentioned risks support expectant management. On the other hand, oocyte retrieval associated risks, the possibility of missing occult malignancy and endometriosis progression due to ovarian stimulation remain unsolved obstacles in front of conservative management advisors. The alternative options for endometriomas away from surgery and conservation include medical treatment and ultrasound-guided aspiration. Whereas prolonged gonadotropin-releasing hormone (GnRH) agonist down-regulation may be beneficial, data on ultrasound aspiration are more controversial.60-63

In fact, this surgery can actually reduce IVF pregnancy rates, because every time endometriotic tissue is removed from ovaries, normal ovarian tissues are also sacrificed at the same time. This reduces ovarian reserve, and can end up in growing few oocytes and getting only a few embryos to transfer.64,65

Ovarian Drilling Prior ART

Recently, laparoscopic ovarian drilling (LOD) has been used widely by gynecologists as an alternative surgical method for ovulation induction using gonadotropins for polycystic ovary syndrome (PCOS) patients unresponsive to clomiphene, but there is a lack of consensus on effectiveness of this method.66,67

Dale et al64 conducted a study on the effectiveness of LOD on insulin resistance and pregnancy rate in patients with PCO. They followed patient for 12-18 months where they found that following ovarian drilling the non-insulin-resistant women more frequently achieved a regular menstrual cycle and ovulation than the insulin-resistant PCOS women. Consequently 18 (50%) of the non-insulin-resistant PCOS women achieved a pregnancy versus only five (18%) of women in the insulin-resistant PCOS group. Following treatment with both ovarian drilling and IVF, 27 cases (75%) of the non-insulin resistant PCOS women achieved a successful pregnancy, while 13 (46%) of the insulin-resistant PCOS group achieved pregnancy. They concluded that further studies are needed to evaluate the effectiveness of LOD in PCO patients resistant to ovulation induction.
Eftekhari et al\textsuperscript{19} conducted a retrospective study to evaluate the IVF/ICSI outcomes in clomiphene-resistant women with PCOS who were treated with LOD. They found that ovarian cauterezation before IVF/ICSI in patients with PCOS reduced the risk of OHSS ($p=0.025$). Despite the same pregnancy rate in both groups ($p=0.604$), more obtained oocytes and embryos were seen on women without ovarian drilling than women with LOD ($p=0.001$ and $p=0.033$, respectively).

Another retrospective study was conducted by Cai et al\textsuperscript{20} to determine if history of undergoing LOD affects cumulative ongoing pregnancy rates following IVF in patients with PCOS. The study included 110 patients in the LOD group, 127 patients in the no-LOD group, and 990 patients in the age-matched group. A lower number of retrieved oocytes, fewer available embryos, and a lower number of cryopreserved embryos were observed in among patients in the LOD-group compared with the other groups ($p<0.001$). They concluded that LOD could compromise cumulative ongoing pregnancy rates during subsequent IVF.

Bosteels et al\textsuperscript{21} conducted a review study on the role of reproductive surgery prior to ART. They found that LOD results at least in equal pregnancy rates as gonadotropin treatment (RR 1.0, 95% CI 0.83-1.2) but decreases the multiple pregnancy rate (RR 0.16, 95% CI 0.04-0.58).

### Ovarian Tissue Transplantation

Ovarian cryopreservation is one of fertility preservation methods in women who wish to conceive, the current and proven method is to graft the frozen-thawed ovarian tissue into the ovarian fossa or into the remaining and irradiated ovary. Harvesting ovarian tissue could be done laparoscopically.\textsuperscript{77}

The implanted ovarian tissue becomes functional 3-4 months after transplantation and may last up to 3 years, depending on the amount of ovarian tissue transplanted. Accordingly, ovarian transplantation should be carried out only when the patient is ready to conceive.\textsuperscript{78,79}

### Endoscopic Peritoneal Surgery (Laparoscopic Adhesiolysis)

Laparoscopic adhesiolysis is necessary to improve the outcome of the IVF cycle as ovaries may be adherent due to adhesions resulting from conditions such as endometriosis, pelvic infections and previous surgeries. In these situations, a laparoscopic adhesiolysis can help in the breakdown of these adhesions and free the ovaries.\textsuperscript{80}

### Laparoscopy and IVF/ICSI are Complementary Since a Long Time

The first IVF child ensued following laparoscopic ovum retrieval. In modern practice, laparoscopic egg retrieval is still required whenever inaccessible ovaries are encountered.\textsuperscript{81}

### CONCLUSION

Endoscopic reproductive surgeries should replace open surgeries and should be the first choice in women with lesions in the tubes, uterus, ovary or peritoneum affecting fertility. With expert hands, endoscopic reproductive surgeries remain superior to ART being less costly and with minimal complications.

### CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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