Endometriosis is an enigmatic and progressive benign gynecological condition with protean presentations and overlapping clinical manifestations. It may be found in up to 40-50% of women presenting with infertility and 5-10% of fertile women. Proposed classifications are frequently non-reflective of the actual clinical impact of the disease in women. Because of the absence of proper standardization for severity and progression and the availability of a wide array of treatment options, meaningful interpretation of the medical literature on this subject may prove to be very difficult. The multifactorial nature of the mechanisms by which the disease manifests itself and affects clinical outcome has also rendered this task even more complex.

A debated and still controversial subject in this context is whether endometriosis should be treated prior to Assisted Reproductive Technology (ART) cycles.

The merits of the surgical treatment of endometriosis on ART outcome

Unfortunately, randomized controlled trials specifically aimed to investigate whether surgical treatment prior to ART improves the final reproductive outcome in endometriosis-associated infertility are currently lacking. Alternatively, investigators have attempted to establish benefits of the surgical treatment by using various retrospective study designs, all of which remain short of being conclusive because of inherent limitations intimately linked to the nature of such investigative strategies.

Most studies have focused on the surgical management of women with late-stage endometriosis and ovarian involvement in relation to the ART outcome. In a case-control study, Garcia-Velasco et al. (1) compared the ART performance of women who underwent laparoscopic cystectomy for an endometrioma (≥3 cm in size) with those with an existing endometrioma of similar size who never had surgical treatment. They showed that laparoscopic cystectomy prior to ART did not improve the number of oocytes collected, number of embryos obtained or pregnancy rates. Women who underwent surgical excision required significantly higher doses of gonadotropins and achieved significantly lower peaks of estradiol on the day of human chorionic gonadotropin injection. Proceeding directly to ART in women with an asymptomatic (<3 cm) ovarian endometrioma reduced both the time and cost to pregnancy. Wong et al (2) also failed to demonstrate a statistically significant improvement in

Comment by: Johnny Awwad, M.D.
Beirut, Lebanon

Efstratios M Kolibianakis, M.D.
Basil C Tarlatzis, M.D.
Unit for Human Reproduction,
1st Department of Obstetrics and Gynaecology,
Aristotle University of Thessaloniki
E-mail: stratis.kolibianakis@otenet.gr

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reproductive outcome following ART in women who underwent laparoscopic cystectomy for endometriomas in comparison to those who did not have their endometrioma operated prior to the procedure.

Evidence therefore favors a lack of benefit from surgical treatment of late-stage endometriosis in improving the final outcome of ART cycles. Conversely, surgical treatment of endometriomas could potentially incur damage to healthy tissues and concerns for a reduction in ovarian reserve has been entertained and documented by numerous retrospective studies.

In a case-control study, Al-Azemi et al (3) compared the ART reproductive outcome of women with surgically proven 'mostly surgically treated' endometriomas and women with tubal infertility. While cumulative pregnancy and live birth rates were comparable amongst both groups, women with ovarian endometriosis expressed a significantly poorer ovarian response, more gonadotropin consumption and a progressive decline in ovarian reserve over time shown by a poorer response with each subsequent cycle despite significantly higher gonadotropin doses used. Tinkanen and Kujansuu (4) also demonstrated a higher number of embryos available for transfer and a higher clinical pregnancy rate in women with a recurrent endometrioma following previous surgical treatment, compared to women with no recurrences following surgery. The lack of recurrence was attributed to the more extensive and radical nature of the surgery in these women that likely resulted in diminished ovarian reserve. More investigators confirmed a reduced number of retrieved oocytes following surgical treatment of endometriomas (5,6).

Considering the limitations of the retrospective study design, a more reliable means of assessing the influence of surgery on ovarian function consists of using the unaffected contralateral ovary of the same woman as control. Using this approach, at least two groups of investigators observed a significant reduction in the number of follicles in response to stimulation in the affected surgically treated ovary (7,8).

Still other investigators failed to confirm a negative effect of ovarian cystectomy on the reproductive outcome of ART in women with endometriomas. Donnez et al. (9) in their retrospective analysis of women with endometriomas treated with laparoscopic vaporization of the cyst wall, found a similar ART outcome to women with tubal factor infertility. Using paired comparisons, they also demonstrated similar ovarian responses in cystectomized ovaries compared with the contralateral nonoperated ovary. These findings emphasize the heterogeneity of the surgical approach utilized and the surgical expertise of the operator. Vaporization of the cyst wall could represent a more conservative and better suitable surgical approach in women with endometriomas who are candidates for future ART treatment. Canis et al. (10) in a retrospective analysis also found no reduction in oocytes collected and embryos obtained in women who underwent laparoscopic cystectomy for an endometrioma >3 cm compared to those with early stage endometriosis and tubal factor infertility.

The merits of the medical treatment of endometriosis on ART outcome

A series of studies have investigated the potential benefits of prolonged pituitary suppression using gonadotropin-releasing hormone agonists (GnRH-a) over the reproductive outcome of ART in women with endometriosis.

In a prospective randomized trial, Surrey et al (11) demonstrated that a three-month pituitary suppression utilizing a GnRH-a administered immediately prior to controlled ovarian hyperstimulation, significantly improved ongoing pregnancy rates after ART in women with endometriosis-associated infertility compared to standard controlled ovarian hyperstimulation regimens. No deleterious effect on ovarian response was observed. More than 2/3 of women in the study group had advanced stage III/IV endometriosis. Using a nonrandomized design, Nakamura et al (12) found that the administration of GnRH-a for more than 2 months prior to ovarian stimulation increased significantly pregnancy rates but increased the need for higher gonadotropin doses compared to standard mid-luteal GnRH-a down-regulation in women with endometriosis. These findings were also supported by other investigators (13-14).
For early-stage disease however, the findings were less conclusive. In a prospective randomized trial, Remorgida et al. (15) demonstrated a non significant trend towards higher pregnancy rates in women with early stage I-II disease undergoing gamete intrafallopian transfer, when GnRH-a pituitary down-regulation for 6 months was compared to standard or no down-regulation.

The above findings suggest the presence of evidence, though limited, to support a beneficial role for prolonged GnRH-a suppression on improving the ART reproductive outcome of women with late-stage endometriosis-associated infertility. This is in contrast to evidence strongly suggesting a lack of benefit for medical therapy in improving spontaneous conception rates in these women (16). It is possible that the potential benefits of prolonged GnRH-a therapy are short lasting, and rapidly reversible with the discontinuation of the treatment. Controlled ovarian stimulation and ovum pick-up performed immediately following prolonged medical therapy, may allow the patient the greatest chance of conception while associated hostile peritoneal environment may still be maximally suppressed.

CONCLUSION

Based on 'level B evidence', the surgical treatment of endometriosis prior to ART cycles does not appear to improve the reproductive outcome in women with endometriosis-associated infertility. Surgical treatment of asymptomatic late-stage endometriosis with ovarian involvement could nevertheless compromise ovarian reserve and decrease ovarian response to stimulation. Vaporization rather than excision of the endometrioma cyst wall may represent a more conservative and better suitable alternative for symptomatic women who are candidates for the ART treatment.

Based on limited 'level A evidence', prolonged GnRH-a pituitary suppression prior to the ART cycle appears to improve significantly reproductive outcome in women with late-stage endometriosis-associated infertility.

REFERENCES

The identification of ectopic "endometrial-like" tissue was first described by Sampson and Cullen in the 1920's (1). This initial finding fueled research into the complex pathology of endometriosis, in addition to treatment modalities that may be employed to reduce associated symptomatology, including pelvic pain and dysmenorrhea, as well as the suspected detrimental impact on fertility.

According to the most recent Center for Disease Control (CDC) report on Assisted Reproductive Technology (ART) statistics, six percent of all women seeking ART have been diagnosed with endometriosis. In total, almost 87,000 fresh cycles from non-donor oocytes are performed in the United States annually, in addition to over 15,000 frozen embryo transfers (2). Through the use of simple mathematical computation, the number of patients suffering from endometriosis and seeking in vitro fertilization (IVF) is approximately 6,120, not to mention those who have been labeled with the diagnosis of "male factor" or "unexplained infertility" and directed to IVF without completing the laparoscopic evaluation to investigate for a peritoneal factor.

Barnhart et al. performed a meta-analysis on twenty-two published studies, ultimately concluding that patients with endometriosis-associated infertility undergoing IVF have pregnancy rates that are almost half that of women undergoing IVF for other reasons (3). Aboulghar and colleagues supported these findings in a case-controlled study highlighting a detrimental impact of stage IV endometriosis on IVF outcome even after surgical intervention as compared to age-matched controls with tubal factor infertility (4). More recently, Kuivasaari et al. conducted an observational study, reporting a significantly lower pregnancy rate among women with stage III/IV endometriosis (22.6%) compared to stage I/II (40%) or tubal factor infertility (36.6%) (5). These findings support further investigation into not only the pathophysiologic mechanisms of the disease, but means by which we as clinicians may impact this particular patient population in a beneficial manner.

With reductions in IVF success compared to controls, the question that is most perplexing is whether women with multiple IVF failures or sonographic evidence of an endometrioma would benefit from surgical therapy prior to controlled ovarian stimulation? Furthermore, would patients labeled with the diagnosis of "unexplained infertility" with an incomplete fertility evaluation and repeated IVF failures benefit from a laparoscopic evaluation and treatment of endometriosis if discovered? In order to address these issues, it is important to explore the potential benefits from an evidence-based perspective and critically appraise the available literature.

First, Surrey and Schoolcraft performed a retrospective analysis in patients with the primary diagnosis of endometriosis undergoing IVF, all of whom had surgical therapy for endometriosis in the preceding 60 months. Patients were subdivided into whether or not the surgical procedure occurred more or less than six months from transvaginal oocyte aspiration. Regression analyses revealed no correlation between implantation rates and the interval between surgical intervention for endometriosis and transvaginal oocyte aspiration. Regression analyses revealed no correlation between implantation rates and the interval between surgical intervention for endometriosis and transvaginal oocyte aspiration. They concluded that any enhancement in reproductive function that is gained through surgery in spontaneous conception is most likely overcome by the greater impact of the implementation of IVF (6). This publication is contrasted to the recent findings of Littman et al. in