

Trans Vaginal Hydrolaparoscopy can Rule Out Ovarian Cancer in High-risk Women Interested to Preserve their Fertility - A Pilot Study

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Abstract

Direct visualization of the ovaries and tubal fimbria by Transvaginal hydro-laparoscopy (TVHL), in high-risk Ovarian Cancer (OC), patients, could further support and augment the existing screening tests of early OC diagnosis. Between 2005 and 2017 TVHL and hysteroscopy were performed in 67 asymptomatic patients at high risk of OC, interested to preserve their ovaries and fertility, and denied undergoing preventive bilateral salpingo-oophorectomy (BSO). Forty-five patients had an infertility problem over 6 months and were interested in getting pregnant as soon as possible. All patients had normal Ca-125 and TVU scanning results except in 12 patients an endometrial lesion was detected.

Excellent visualization was achieved in 64/67 (96%) cases examined. The average time of TVHL was 35min. Sixty-two (93%) patients found TVHL a simple and painless procedure. In 3/67 (0.45%) patients one of the two ovaries' direct visualization was compromised due to adhesions and standard laparoscopy was recommended. In 5/67 (0.75%) cases the clarity was not optimal, and the normal saline injected in the pelvic cavity was exchanged with a fresh one. All patients had cytology of pelvic washing, 25 patients had ovarian biopsies and 13 patient's tubal fimbria brushing for cytology. One case of epithelial ovarian cancer, one case with a borderline ovarian tumor, three cases with simple and one with complex endometrial hyperplasia were diagnosed after histopathological examination in these selected series of patients.

This pilot study demonstrated excellent patients' compliance, minimal complication rate, high diagnostic accuracy, and detection of subtle lesions, ability to take ovarian biopsies, tubal fimbrial brushing, and collection of pelvic washings for cytology. The introduction of TVHL to the existing standard Ca 125 and TVU scan screening program for high OC patients interested to preserve their fertility may potentially improve safety and early OC detection. A prospective randomized control trial is needed to prove and support further this proposal.

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Introduction

Retrograde menstruation exposes regularly, both the tube and the ovary to inflammatory agents. It has been postulated that microtrauma on the ovarian epithelium allows for the exfoliated tubal cells to be embedded in the ovarian stroma, increasing the risk for ovarian carcinoma (OC) [1]. This theory is further supported by the beneficial effects of tubal ligation and the oral contraceptive pill. Tubal ligation stops retrograde menstruation; reducing ovarian cancer incidence. The oral contraceptives, suppress ovulation and reduce the amount of retrograde menstrual bleeding, hence preventing the ovarian surface from microtrauma and inhibiting the seeding of cells into the ovarian stroma; reducing the risk of serous epithelial OC [2,3].

Transvaginal hydro-laparoscopy (TVHL) is a minimally invasive technique that resembles other endoscopic procedures like colonoscopy and bronchoscopy. TVHL can examine the ovarian

epithelium from close-up views and enable biopsies from suspected pathologies. It was first introduced as a routine clinical practice in 1997 and mainly for infertility and pelvic pain diagnosis. It is a simple, low-cost technique that is highly informative and efficient and has a low risk of complications. Great experience has been gained using TVHL as a technique for infertility diagnosis. Magnification, tissue floatation, and direct visualization of the uterus, adnexa, and fossa ovarica, as well as fibrososcopy and entry to the tubal endolumen, give a diagnostic advantage of TVHL over standard laparoscopy and especially in identifying subtle lesions [4,5].

Women with BRCA mutations or with the mismatch repair genes, MLH1, MSH2, and MSH6, have an increased risk of getting OC at an early age, and therefore, many do not conclude their family planning. It is current practice that ovarian cancer screening using a combination of Trans Vaginal Ultrasound (TVU) scan and Ca-125 testing is initiated between ages 30 and 40, although it is not clear whether it decreases



the mortality rate of women at inherited risk [6]. Hence, in 2004 we suggested the addition of TVHL as a screening test in ruling out OC for high-risk women interested to preserve their fertility [7].

The reliability and efficacy of TVHL examination, in excluding OC in high-risk patients who wanted to preserve their fertility and /or treat their infertility problem was investigated.

Patients

Between 2005 and 2017 TVHL and hysteroscopy were performed in 67 asymptomatic patients at high risk of OC, interested to preserve their ovaries and fertility, and denied undergoing preventive bilateral salpingo-oophorectomy (BSO). All patients had a free, history of abdominal and pelvic adhesions, symptoms of deep infiltrating endometriosis, and free Pouch of Douglas as examined by TVU scan. Forty-five patients had an infertility problem over 6 months and interested to get pregnant as soon as possible. The great majority of these patients expressed feeling upset and insecure concerning their follow-up which included the current available OC screening methods of serum Ca-125 and TVU.

The following high-risk OC patients were recruited to participate in this pilot program. Twenty-six patients diagnosed with breast cancer younger than 40 years of age, 18 women with a history of breast cancer before age 50, and with one or more close relatives diagnosed with breast or OC. Additionally, 23 women with two or more close relatives diagnosed with breast and/or ovarian cancer before age 50 participated in the study. All the above patients had normal Ca-125 and TVU scanning results except in 12 cases, thickened endometrium or suspected polyp/s were reported. Twenty-three patients had myometrial lesions with fibroids and/or adenomyosis. All breast cancer patients were disease-free and 5 years after their diagnosis. A total of 23 patients were receiving tamoxifen.

Method

Patients were placed in a straight level and lithotomy position after sedation with propofol and laryngeal mask. All patients underwent hysteroscopy and Hystero-Contrast Sonography before TVHL, evaluating the endometrium and myometrium by inspection and sampling biopsies. In nine patients one polyp, in three patients two polyps, and in further four patients a septum resected using 5Fr scissors.

The cervical posterior lip was then grasped with a tenaculum. Using the STORZ TVL system (Figure 1) and by holding the cervix with the tenaculum, the spring-loaded Verres needle was injected in the

posterior vaginal vault about 2 cm below the cervical-vaginal junction pointing towards promontory.

The needle was then removed, and a 30° optic of 2.8 mm Bettocchi hysteroscope was introduced in the TVL sheath, connected to a light source and a monitor, verifying the position of the telescoping tip within the pelvic cavity. Once reassuring the optic was within the pelvic cavity, 300 ml of warm normal saline (0.9% NaCl solution) was injected using an automated pump system “Hysteromat” enabling visualization by floatation and separation of the organs and enhancing the clarity of images. Identification of the posterior uterine wall is considered the first step to navigate to the next tissue and organ targets.

Systematic examination of the pelvis by TVHL was performed as demonstrated in (Table 1). Rotating the optic, the right tube could be visualized and was followed until reaching its fimbrial end. Examination of the tubal fimbria and ampule was facilitated by maneuvering the telescope and by using the hysteroscope outflow valve to control the speed of normal saline flow. Occasionally, a grasper was used to enable the entry of the optic into the fimbrial ampulla. The right fossa ovarica, ovarian epithelium, and parietal peritoneum were also meticulously observed and suspicious lesions were noted and biopsied (Figure 2).

Using the operative TVL instruments with a working channel, a 5^{Fr} grasping and either biopsy forceps or brush for cytology were used to perform tubal cytology and/or biopsies of suspicious ovarian epithelium areas. In 13 cases, ‘Cook Medical’ tubal brush was used to collect cells from the tubal end for standard cytologic examinations and immunocytochemistry for Ki67 and p53. Additionally, tubal patency was examined using methylene blue dye. Similarly, the left adnexa, parietal peritoneum, and pouch of Douglas were examined. Bowel loops, part

Table 1: Systematic examination of the pelvis by TVHL. The following structures and organs were examined.

| |
|----------------------------------------------------------|
| entry - first view |
| posterior part of the uterus |
| right adnexa / left adnexa |
| fallopian tube, Fimbria, Ampule, Lumen |
| ovarian ligament |
| fossa ovarica |
| ovary |
| parietal peritoneum |
| anatomical positions and relation between various organs |
| pouch of Douglas |
| appendix |
| bowel |
| Omentum |



Figure 1: TVHL Instruments.

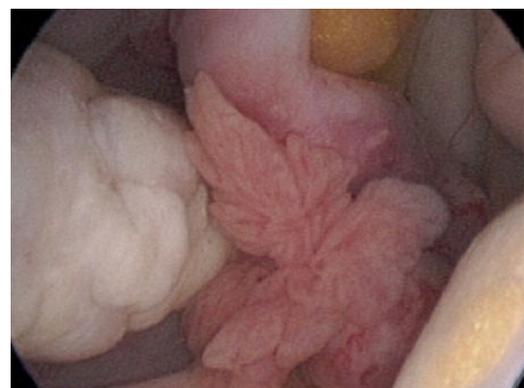


Figure 2: Right Fimbria and ovary examination view, by TVHL.



of the omentum, and often the appendix was also very well visible. At the end of the procedure, the normal saline used for the TVHL was collected back into a sterile container and send to cytological examination for cancer cells. All patients were hospitalized in day care set up, staying in the hospital for several hours, and discharged home in good condition.

Results

The average age of the patients was 34.5 years (26–43) and 16/67 (24%) had at least 1 child. Excellent visualization was achieved in 64/67 (96%) cases examined. The average time of TVHL was (25-45) 35 min. Sixty-two patients found TVHL a simple and painless procedure. In 3/67 (0.45%) patients one of the two ovaries' direct visualization was compromised due to adhesions and standard laparoscopy was recommended. In 5/67 (0.75%) cases the clarity was not optimal, and the normal Saline solution injected in the pelvic cavity was exchanged with a fresh one. No bowel perforation was noted in these series. All patients had cytology of pelvic washing. Twenty-five patients had ovarian and/or peritoneal biopsies (Figure 3) and in 13 patients a cytobrush was used for tubal cytological examinations for Ki67 and p53.

The number of patients and the type of pathologies diagnosed are presented in (Table 2). One case of epithelial ovarian cancer (Figure 4), one case with a borderline ovarian tumor, three cases with simple and one with complex endometrial hyperplasia were diagnosed after histopathological evaluation in these selected series of patients.

Table 2: Trans Vaginal Hydro-laparoscopy findings.

| Diagnosis | Patient Number |
|--------------------------------------------------------------------------------------|----------------|
| Normal pelvic cavity (Tubes and ovaries within normal limits) | 25 |
| Pelvic congestion syndrome (bilateral adnexal varicose veins) | 1 |
| Pelvic adhesions | 12 |
| Peritoneal Endometriosis | 9 |
| Bowel endometriosis | 3 |
| Benign subtle lesions (accessory tubes, fibrial sacculation small paraovarian cysts) | 8 |
| One sided tubal obstruction | 5 |
| Bilateral tubal obstruction | 15 |
| Hydrosalpinx (inspection of endolumen) | 3 |
| PCOD (porcelain appearance) | 7 |
| borderline ovarian tumor | 1 |
| ovarian cancer | 1 |

*Some patients had more than one finding.



Figure 3: Ovarian biopsy.

Discussion

TVHL is a minimally invasive surgery performed in a daycare setting. It is an attractive, highly efficient diagnostic procedure of low cost [8]. Operative TVHL has been identified for its use for subtle pelvic lesions such as ovarian biopsies and drilling in PCOD patients, bipolar fulguration of focal endometriosis, and excision of light adhesions [9,10]. Our results demonstrate the application of TVHL as a feasible method for exploration and revision of the pelvic cavity and ovaries in patients at high risk of OC. Additionally, our patient cohort demonstrated high tolerance reliable results, and minimal complications. TVHL facilitated the close-up inspection of the adnexa, biopsies from suspicious areas, and the collection of pelvic washings for cytology, ruling out OC. One case with an ovarian tumor of low malignant potential and one case with epithelial OC were identified (Figure 4). Infertility symptoms were diagnosed and managed in all



Figure 4: Image of Ovarian cancer.

cases according to each, individual's problem.

Women with inherited risk (BRCA1 carriers) or with the mismatch repair genes (mutations in MLH1, MSH2, MSH6) as well as those with a familial predisposition to OC (first-degree relatives with BOC) carry a relative risk for OC of more than six times greater than that of the general population [6]. Unfortunately, the current recommendation to prophylactic BSO is not appropriate for women who did not complete their family planning either for women with increased risk for cardiovascular accidents and/or cerebrovascular accidents due to deprived estrogens and early arteriosclerosis. In addition, the use of Ca-125 and TVU for screening and monitoring the high-risk women for OC is doubtful regarding its effectiveness and reliability to early disease diagnosis [6].

OC arises from the ovarian surface epithelium lining the ovarian tissue clefts. The normal ovarian cells are squamous or cuboidal which transform to a more columnar shape. Defective cells are trapped within the ovarian stroma forming inclusion cysts – preneoplastic lesions. Cells lining the inclusion cysts become dysplastic, proliferate, and transformed into cancer [1-3]. The advantage of the TVHL to diagnose subtle lesions [5,8], makes it an ideal technique to investigate the ovarian epithelium and tubal ampule for early diagnosis of cancer cells and potentially the chance of diagnosis in the pre-neoplastic stage.

It has been shown that the tube is the causal factor of high-grade serous ovarian carcinoma development, probably related to retrograde menstruation and microtrauma of the ovarian surface [1,2]. In patients with familiar ovarian cancer, the fimbrial end was the most prevalent site for early adenocarcinoma [11]. The incidence of tubal epithelial dysplasia in patients with BRCA mutation genes was 50% while tubal intraepithelial carcinomas were located predominantly at the fimbrial end [12,13]. The use of Fallopian tube cytology has been described in the exploration of patients with fertility problems for the detection of



Chlamydia salpingitis and in patients with endometriosis [14,15]. Lum D, et al. (2014) [16] described the use of cytobrush via hysteroscopy and laparoscopy to collect tubal epithelial cells for cytopathology as an early screening test for ovarian cancer. Gordts S, et al. (2017) reported the efficacy of TVHL visually guided sampling of fimbria cells with the use of cytobrush examining p⁵³ and Ki⁶⁷ [17]. Subsequently, the use of colposcopy and colonoscopy directed biopsies for early cervical and colon cancer diagnosis, provide a great example of how to direct visualization of the ovaries and tubal fimbria by TVHL, in high-risk patients, could provide early OC diagnosis. Within this context, TVHL could further support and augment the existing screening tests of early OC detection in these high-risk women similarly to the screening strategy of cervical and colon cancer early diagnosis.

Furthermore, the learning curve of TVHL is relatively short [18] and the complication rate is low [19]. In a series of 1103 patients with infertility and pelvic pain performing TVHL in an out-patient setup, 92.2% of the cases reported complete pelvic evaluation. The main complications were rectum perforation 0.9%, bleeding of the vaginal wall requiring intervention 0.4% and hospital admissions due to pain 0.2%, and pelvic inflammatory disease 0.4%. The average pain score was rated 4.0 (+2.4 SD) on a VAS from 0 to 10 with 0 meaning no pain at all with no difference in different types of pain relief. Acceptability was rated 1.5 (+2.1 SD) [19]. Rectum perforation although at a very low incidence, is considered TVHL's main complication, remains asymptomatic, and can be managed conservatively with oral antibiotics and remote follow-up [4,7,8].

Given the limitations of OC screening, including the substantial risks of both false positive and false negative results, risk-reducing salpingo-oophorectomy should be considered upon conclusion of childbearing by women with documented inherited predispositions. Although it is not clear that OC screening will significantly decrease the mortality of women at inherited risk, those with OC mutations in susceptibility genes should undergo TVU scan and Ca-125 testing [20]. This pilot study results demonstrate that TVHL permits a meticulous investigation of the ovaries and tubal fimbria, ovarian biopsies, and fimbrial smears cytology in high-risk OC patients, interested to preserve their fertility. We propose a multicenter prospective randomized control study of TVHL in high-risk OC patients and invite all interested colleagues to participate.

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