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Transvaginal endoscopic adnexal sampling

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Abstract

Study objective: To evaluate the feasibility of aspirating and brushing the adnexal structures via transvaginal approach to obtain specimens adequate for cytopathology

Design: prospective feasibility study (Design Classification: Canadian Task Force II-1)

Setting: A tertiary care community-based teaching hospital.

Subjects: Patients who presented for scheduled surgical excision of the adnexa

Interventions: A total of seventeen samples were obtained from the ovaries and fallopian tubes of five patients who underwent laparoscopic adnexectomy. During the indicated procedure, culdoscopic sampling of the adnexa was performed.

Results: Thin prep slides were prepared and analyzed. All patients underwent attempted transvaginal sampling of the ovary and oviduct. The first patient case was complicated by morbid obesity and pelvic adhesions and thus had sampling limited to one ovary. The next four patients had successful sampling of bilateral fallopian tube lumen and ovarian surface. Thus, seventeen samples were available for analysis. All cytologic findings were consistent with final histopathologic review of the explanted organs.

Conclusions: The transvaginal approach can be performed to obtain adequate cytologic samples from the adnexa in situ

Introduction

The 5-year survival for high grade ovarian serous carcinomas (HGSOC) has not improved despite advances in treatment. In fact, this disease remains the most lethal gynecologic malignancy [1]. This is likely because the majority of patients present with widespread disease. An opportunity exists for early detection of localized lesions with anticipated enhanced therapeutic response resulting in improved survival [2].

Detection strategies focused on recognition of pre-cursor lesions have resulted in survival improvements in cancers of the cervix and gastrointestinal tract [3]. The predominant cancers in these sites are epithelial; similar to the most lethal ovarian sub-type. Early detection of HGSOC, and its precursors, might be modeled after the types of screening performed for these more common epithelial malignancies.

Recently gynecologists have focused on the distal fallopian tube/oviduct as the locus for development of pre-malignant lesions that ultimately migrate to the ovarian surface [4]. Evidence suggests that progression to cancer likely takes years, hence there is an opportunity for early detection [5,6].

There is a growing body of literature confirming the reliability of techniques such as imprint cytology and surface brushings that provide ovarian samples for cytopathologic analysis. Unlike with cervical and colonic disease, these samples have been unavailable without performing invasive procedures that typically require general anesthesia and organ excision [7,8].

Several authors have employed minimally invasive techniques (e.g. hysteroscopic, laparoscopic and transvaginal) to obtain in situ adnexal tissue [9,10]. The advantage of these procedures would be the ability to obtain samples without organ removal. Unfortunately, the hysteroscopic approach has failed in attempts to obtain specimens from the distal fallopian tube [9]. Laparoscopy has been successfully employed to access this region, but only under general anesthesia [9]. The transvaginal, culdoscopic, technique is promising to overcome these challenges because it has already been reported to be well tolerated with only sedating anesthetics [11]. Although in the current study, the culdoscopy occurred under general anesthesia, it is anticipated that this procedure will be completed under sedation in follow-up investigations.

This study was conducted to evaluate the feasibility of obtaining both ovarian brushings and distal oviduct aspirates transvaginally. One previous limitation to the culdoscopic approach is that there was no commercially available instrumentation to obtain specimens from both the ovarian surface and the distal fallopian tube lumen. This study describes a tool specific for this task. The objective was to provide samples adequate for cytopathologic analysis. Having accomplished this we anticipate performing future studies to explore the use of this type of specimen to identify HGSOC precursor lesions.

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Materials and methods

This is a prospective feasibility study approved by the Saint Francis Hospital and Medical Center Institutional Review Board (IRB). Study subjects include women undergoing laparoscopic adnexal excision, with or without hysterectomy, by a minimally invasive approach. Study subjects had surgery for benign or malignant gynecologic indications. Patients under 18 years of age and pregnant patients were excluded from the study. All patients completed informed consent. Demographic, clinical, operative and pathologic details were recorded.

Currently there are no existing devices to collect both oviduct aspirates and ovarian surface brushings. We created a collection tool that would traverse the operating channel of a standard ureteroscope. We also devised a balloon that could be inserted vaginally to elevate the uterus away from pelvic viscera and sidewall vessels. The balloon has a channel through which the ureteroscope was then passed.

We completed the procedure as follows:

After administration of a general anesthetic, the patients are placed in dorsal lithotomy position. A speculum is placed, the cervix is visualized and grasped with a tenaculum. The avascular space in the cul de sac is pierced with a 5 mm laparoscopic port.

The balloon is inserted and insufflated, the scope is advanced through the balloon channel to the uterine fundus. The oviduct is examined from the cornua to the distal fimbria. The adjacent ovary is inspected by flexing the scope tip. Sequential sheaths then allow for use of the same collection tool to sample both regions of the adnexa while maintaining the specimens in separate compartments. The ovarian surface is brushed and the brush is retracted into an inner protective sheath to prevent specimen loss during manipulation. The outer sheath is connected to a syringe at the surgeon end and is fenestrated at the operating tip. The fenestrated tip is passed into the tubal lumen, suction is applied with the syringe and the resulting aspirate is maintained in the separate outer chamber surrounding the brush in the inner chamber. Thus one device is used to sample the tube and the ovary, in either order, with both specimens protected from tissue cross-contamination. Once removed from the ureteroscope the ovarian brush is advanced, cut and placed in standard pathology collection cups. The syringe is filled with Cytolyte and the outer chamber is flushed to produce the tubal aspirate specimens in a separate collection tube. A second device is then introduced to sample the contralateral adnexa. The balloon is decompressed and extracted prior to port removal.

Our specimens from the ovarian brushings and fallopian tube aspirates were transferred in ThinPrep CytoLyte solution (Hologic Inc.) The specimens were centrifuged and filtered to prepare ThinPrep slides and then papanicolaou stained. These were inspected for the presence or absence of epithelial cells and compared to surgical specimen adnexal cells by a gynecologic pathologist (A.J.). Immunohistochemical staining of a subset of the specimens was also performed. As no current standard for adnexal tissues exists, the College of American Pathologists guidelines for other epithelial tissues were applied to determine specimen adequacy [12].

Outcome variables included adnexal accessibility, successful sampling via culdoscopic approach and a sample yield adequate for traditional cytopathologic techniques.

Results

Our operating times ranged from 6-45 minutes. The initial case was the longest and an outlier. The remainder of the study collections were completed in less than 15 minutes.

The culdoscopy approach successfully produced specimens from all subjects (Table 1). Four patients (A, B, C, E) underwent robotic assisted laparoscopic hysterectomy with bilateral salpingo-oophorectomy and patient (D) underwent single incision bilateral salpingo-oophorectomy. Unilateral ovarian sample was obtained from the first patient (A). This was the first use of the instrument and the study procedure was terminated early due to concerns about extended OR time. All remaining patients had successful bilateral adnexal visualization and sampling.

We obtained a total of 17 specimens from the 5 subjects. Patient (A) had one ovarian surface brushing specimen collected. The following four patients (B, C, D, E) had bilateral ovarian surface brushings and bilateral distal fallopian tube aspirate collections. Each of the 17 specimens was submitted for cytologic examination and had satisfactory cellularity for interpretation. The cytology findings correlated with final histopathology in all cases. In the ovarian samples there were ranges of 5 to 14 groups of cells. In the fallopian tube aspirates there were ranges of 2 to "numerous" "sheets" of cells. All but one had at least 5 groups of cells (Table 1).

Patient B was a BRCA-1 gene mutation carrier whose final pathology specimens did not exhibit the p53 signature. Her ovarian brushing specimen contained ample tissue for p53 staining which also returned negative for p53 signature.

Patient E, whose final diagnosis was Endometrial Adenocarcinoma FIGO grade 1, also had unilateral salpingitis on final histopathologic analysis. This patient's corresponding ipsilateral fallopian tube aspirate detected a background of inflammatory cells while the contralateral tubal sample did not (Table 1: specimen numbers E2 & E4).

There were no cases of bleeding or organ perforation during the culdoscopic portion of the surgery. Laparoscopic visualization of the adnexa during sampling confirmed intact, viable organs. The scheduled operations were subsequently completed without incident. There were no post-operative vaginal complications.

Comments

This pilot investigation utilized transvaginal endoscopy to visualize and successfully sample patients' adnexa. An advantage of this approach is that the organs, and especially the distal fallopian tube, can be readily evaluated in situ. This portion of the tube, the likely source of precursor lesions, has eluded previous attempts at minimally invasive sampling via hysteroscopic approach [9].

The rationale for studying such techniques is that alternative approaches for identification of occult ovarian disease are needed. The currently employed indirect methods of detection, imaging and serum screening, have not resulted in improved survival and are not acceptable for screening [13]. There is evidence of a long precursor state for ovarian cancer and prophylactic surgical removal of the adnexa has at times revealed early or preinvasive disease [14,15]. Investigations have thus far failed to provide a non-extirpating method of detecting these initial changes; thus the standard of care has been to prevent disease in high risk patients by removing the adnexa by the age of 40 years old. The National Cancer Care Network Guidelines include recommendations for serial CA-125 and ultrasound evaluations until such patients reach an age when definitive surgical therapy is acceptable. The guidelines acknowledge that this surveillance mode has never been shown to improve survival even in women at highest risk [16]. A noninvasive screen for preclinical disease detection could be used to reduce the occurrence of invasive cancer. In addition, a negative

Table 1. The culdoscopy approach successfully produced specimens from all subjects

Patient	Specimen number	Patient Diagnosis*	Pathology Report	Aspirate/Brushing Results
A	A1	BRCA 1 gene mutation/CA 125=17.9	cortical inclusion cysts, no evidence of malignancy	7 small groups of benign epithelial cells
B	B1	BRCA-1 gene mutation /CA125=7.8	multiple cystic follicles	5 groups of mesothelial cells
B	B2	BRCA-1 gene mutation /CA125=7.8	no significant histopathologic abnormality of FT	numerous epithelial cells
B	B3	BRCA-1 gene mutation /CA125=7.8	multiple cystic follicles	14 groups of mesothelial cells
B	B4	BRCA-1 gene mutation /CA125=7.8	no significant histopathologic abnormality of FT	sheets of mesothelial cells and numerous epithelial cells
C	C1	stage 1A FIGO 1 EAC endometrioid	mucinous cystadenoma positive CK7/ ER/PR& negative CK20&CDX2	groups of benign mesothelial cells and few epithelial cells
C	C2	stage 1A FIGO 1 EAC endometrioid	paratubal cysts	scattered groups of benign epithelial cells
C	C3	stage 1A FIGO 1 EAC endometrioid	mucinous cystadenoma positive CK7/ ER/PR& negative CK20&CDX2	rare groups of benign epithelial cells
C	C4	stage 1A FIGO 1 EAC endometrioid	paratubal cysts	scattered groups of benign epithelial cells
D	D1	metastatic breast cancer	benign ovary, multiple corpoa Albicantia	few small groups of epithelial and mesothelial cells
D	D2	metastatic breast cancer	benign FT with paratubal cyst	numerous groups and single epithelial cells seen
D	D3	metastatic breast cancer	benign ovary showing endometriotic cysts	few small groups of epithelial cells
D	D3	metastatic breast cancer	benign FT w/Walthard rests	few groups of epithelial cells and single cells seen
E	E1	stage 1B FIGO 1 EAC endometrioid	benign ovary	6-7 groups of benign surface epithelial (mesothelial) cells
E	E2	stage 1B FIGO 1 EAC endometrioid	chronic and focal acute salpingitis	5-6 groups of benign/reactive epithelial cells with a background of inflammatory cells
E	E3	stage 1B FIGO 1 EAC endometrioid	incidental fibrothecoma	6 small groups of benign surface epithelial (mesothelial) cells
E	E4	stage 1B FIGO 1 EAC endometrioid	benign FT	single group of few mesothelial cells; 2 small groups of epithelial cells

FT=fallopian tube; EAC=endometrial adenocarcinoma, ER=estrogen receptor; PR=progesterone receptor; CK7, CK20 & CDX2 are panel markers useful in classifying the histologic type and possible origin of tumors

screen could potentially allow women to safely retain normal organs, preventing morbidity associated with early surgical menopause. The initial step in developing such screening could be to transition from indirect methods of detection, imaging and serum tumor marker measurements, to obtaining samples directly from the organs in situ.

Recently, inspection after removal of surgical specimens has been used to identify local, preinvasive adnexal disease [8]. Imprint cytology methods have also been used to rapidly identify ovarian cells from surgical specimens [7]. This is helpful because pathologists are familiar with the technique, the results of which can be used to guide surgical decision making while a patient is still in the operating theater. This procedure for reviewing samples of the organ surface has a sensitivity of 96.2%, specificity of 75%, positive predictive value of 96.3% and diagnostic accuracy of 83.3% when evaluating ovarian neoplasms [17,18]. However, these techniques require surgical removal of the organs.

Alternatively, surface brushing can be completed in vivo. Because the hysteroscopic approach to access the oviduct has a high failure rate, laparoscopy has been required to consistently interrogate the distal fallopian tube [9,10,19]. Brush cytology of the fallopian tube has been performed via laparoscopy to evaluate patients with infertility. Additionally, subsequent abdominal exploration showed that there was no scarring caused by these procedures [20]. While investigators have determined that this method of cytologic collection of fallopian tube specimens is reliable and safe, laparoscopy typically requires general anesthesia [8,9,19].

Culdoscopy, referred to as transvaginal endoscopy, permits examination of the pelvis without general anesthesia. This minimally invasive procedure is traditionally performed in the office setting [21,22]. A scope is placed through the posterior vagina into the cul de sac and the adnexa is then examined [23]. It has been reported that with experience, the surgeon can even examine the lumen of the oviduct with a rigid scope [24]. Rigid culdoscopy and culdocentesis, which involves sampling of pelvic fluid, were used for most of the last century. Both techniques were essentially abandoned with the development of laparoscopy [22,25]. More recently laparoscopy has been combined with culdoscopy in the operating theater. Natural orifice transluminal endoscopic, NOTES, procedures enable the surgeon to access the pelvis and indeed the entire abdomen during cholecystectomy or appendectomy [26-28]. In this study, the ovaries were carefully inspected with a flexible scope that allowed for the examination of the ovarian surface. Similarly, the fimbriated end of the fallopian tube was visualized. The device permitted us to obtain aspirates from the distal fallopian tubes as well as surface ovarian brushings. As noted above, transvaginal endoscopy has been demonstrated to be well tolerated in the office setting; thus, we would expect to perform these procedures under the sedation in subsequent investigations.

An issue to address in the follow-up studies is specimen analysis. Cytopathologic standards exist for tubal evaluation but not yet for ovarian surface samples. Given the evidence for tubal origin of disease, characterization of in situ tubal specimens has already been described. By definition, precursor p53 signatures are at least 12 cells that stain p53-positive by immunohistochemistry and have a low proliferative index [29]. Although there were no patients in this study that exhibited the signature, in the subset of study samples that were evaluated there was adequate tissue to analyze for the staining. This holds promise for future investigation. Due to the historical inability to sample the ovary in situ, criteria have not yet been defined to determine adequacy of surface specimens. We therefore relied on standards of other epithelial tissues in this study [30]. Future studies will need to include patients with varied pathology in order to establish organ specific criteria for sample adequacy.

This pilot study demonstrated the feasibility of the approach and the acceptability of the samples obtained via culdoscopy. Subsequent studies will be aimed at further developing this approach.

These findings add to the growing body of literature suggesting that in vivo endoscopic adnexal sampling is feasible and safe. Future studies will be performed on patients with benign and potentially malignant pathology to define criteria for sample adequacy of both the ovarian surface and fallopian tube specimens. Ultimately further study may provide useful specimens of precursor lesions that could result in early detection of cancerous states.

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