Impact of human papillomavirus infection on the neovaginal and vulval tissues of women who underwent surgical treatment for Mayer-Rokitansky-Kuster-Hauser syndrome

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Objective: To evaluate the impact of human papillomavirus (HPV) infections on the neovaginal and vulval tissues of women who underwent surgical treatment for Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome.
Design: Multicenter observational study.
Setting: University and community hospitals.
Patient(s): Thirty-three women who had previously undergone neovagina reconstruction due to MRKH and who were referred to our centers for the evaluation and treatment of HPV neovaginal/vulval-related lesions.
Intervention(s): HPV infections were confirmed by polymerase chain reaction analysis or hybrid capture 2 tests; the patients underwent vaginoscopy, pap smear, and biopsy of the lesion and were treated by laser vaporization. Follow-up was conducted for 5 years.
Main Outcome Measure(s): HPV-related neovaginal/vulval lesions, HPV testing, follow-up, recurrence rate.
Result(s): Seventeen patients showed vulval lesions, and 16 patients neovaginal lesions. HPV testing results were positive for low-risk HPVs in 27 patients and high-risk HPVs in six patients. All the vulval lesions were condylomata, whereas 10 neovaginal lesions were condylomata, three were vaginal intraepithelial neoplasia (VAIN) degree 1, two were VAIN degree 2, and one was an adenocarcinoma. Eight patients were lost to follow-up. Twenty patients tested positive for an HPV infection, and seven patients (28%) had a recurrence of the lesion in the follow-up time.
Conclusion(s): Patients who underwent neovagina reconstruction have sexual relationships and are HPV exposed. These patients should be evaluated after surgery for HPV infections to prevent HPV-related diseases and cancers. (Fertil Steril® 2011;96:969–73. ©2011 by American Society for Reproductive Medicine.)

Key Words: Neovagina, Mayer-Rokitansky-Kuster-Hauser syndrome, human papillomavirus

Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome is a malformation of the female genital tract (agenesis of vagina and uterus in the presence of normal external genitalia and normal ovarian function) that has an incidence of one in 4,000 newborns (1–3).

Although conception is irremediably impaired, neovagina reconstruction aims to provide a satisfactory sexual life for these patients.

Over the past century, several surgical and nonsurgical procedures have been proposed for the creation of a neovagina, even though there is no agreement regarding the "best" or "optimal" procedure to choose (4). One of the most used techniques is the reconstruction of a neovagina by the use of a traction device attached to the abdomen, sutured subperitoneally, and a plastic "olive" placed in the vaginal dimple, as proposed by Vecchietti and colleagues in 1965 (5, 6); other surgical treatments are Abbe-McIndoe-Reed vaginoplasty (skin graft procedure) or intestinal vaginoplasty, where segments of the rectum, ileum, or sigmoid colon have been used for vaginal replacement (4).

More recently, several investigators have suggested a number of techniques and devices for minimizing the surgical trauma, such as the use of laparoscopy or tissue engineering procedures (7, 8).

These procedures usually provide good functional and anatomical results, and patients report satisfactory sexual intercourse a few months after treatment (9). Moreover, Vecchietti's technique provides a neovagina with a glycogen-secreting epithelium, similar to the normal and physiological vaginal one (10).

Beside this, the vast majority of the past series focused on the surgical outcome of the neovagina reconstruction, and very little is

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known regarding neovagina-associated diseases, with just a few articles reporting the development of malignant (11–15) or premalignant lesions (16–18) in the neovaginal tissues. A review of the literature in this field suggests that squamous carcinomas occur in skin graft neovaginas, whereas adenocarcinomas occur in intestinal neovaginas (19).

It has been documented that the neovaginal tissues may be infected by the human papillomavirus (HPV) viruses (19, 20), however, there are a lack of data regarding the HPV infections and associated lesions in the neovaginal tissues.

On the basis of this background, we recruited all the neovagina patients referred to our centers for the treatment of HPV-associated lesions with the aim of evaluating the HPV-related diseases, characterize the HPV infections, and follow-up the patients for HPV recurrence after the treatment.

MATERIALS AND METHODS

Patients

Thirty-three women who had previously undergone neovagina reconstruction for MRKH were referred to our centers (Department of Woman's Health and Territorial Medicine, University of Rome La Sapienza; Department of Obstetrics and Gynaecology, Catholic University of the Sacred Heart of Rome; Department of Gynaecologic Oncology, National Cancer Institute of Aviano; Department of Obstetrics and Gynecology, Cristo Re Hospital of Rome) from the January 1989 to December 2005 for the evaluation and treatment of HPV-related neovaginal or vulval lesions and enrolled in a prospective observational study regarding the detection of HPV in patients who had undergone neovagina reconstruction.

Patients presenting with vulval condylomata were included since these lesions are HPV related and thus were in agreement with the aim of the present study.

Women were treated for the MRKH syndrome at other institutions and underwent routine follow-up evaluations after surgical neovagina reconstruction; the patients were referred to our centers because they are second-line referral centers for cervical pathology. They were recruited in an observational study for the assessment and treatment of a possible HPV-related lesion that was recognized in the postoperative follow-up of the neovagina reconstruction.

The study was reviewed and approved by the Institutional Review Board; written informed consent was obtained from all participants for the investigation, treatment, and collection of data.

A structured questionnaire was administered to the patients regarding past medical history and personal habits (surgical technique used for the neovagina reconstruction, age of the patient at the time of surgery, age at the first sexual intercourse, number of partners).

Patients underwent physical examination, vaginoscopy, Pap smear, biopsy of the lesion, vaginal swab, vaginal pH evaluation, and HPV testing.

Vaginoscopy was performed using a Zeiss 50 T colposcope (Carl Zeiss Inc.), after 5% acetic acid application and Shiller test.

The cytological evaluations and histological diagnoses were performed by specialized pathologists of the different centers involved in the study, sharing the same classification systems. The vaginal swabs were cultured for mycete, chlamydia, Gardnerella, and S*treptococcus agalactie,* and patients were tested for *Trichomonas vaginalis* by fresh bacterioscopic examination.

HPV Testing

HPV detection was performed by polymerase chain reaction (PCR) from 1989 to 2001 and using the hybrid capture 2 test (HC2) later.

For DNA extractions, all cytological neovaginal samples were collected in sterile 1.5 mL polypropylene tubes and resuspended in 100 μL of digestion buffer with proteinase K, incubated overnight at 37°C, followed by incubation at 90°C for 5 minutes and resuspension. An aliquot of 10 μL of extraction solution was used for PCR amplification and detection of HPV using the following set of primers: HPV-6/11: 5′-GAC CAG TTG TGC AAG TTTAATC-3′ and 3′-CTT CCA TGC ATG TTG TCC AGC AG-5′; HPV-16: 5′-ACC GAA ACC GGT TAG TATAAAAGC-3′ and 3′-GAT CAT TTG TCT CTG GTT GCA AAT-5′; HPV-18: 5′-CAC ACC ACA ATA CTA TGG CGCGCT-3′ and 3′-CTG CTG GAT TCA ACG GTT TCT GGC-5′; HPV-31/33/51: 5′-TGT CAA AAA CCGTTGTGTCC 3′ and 3′-GAG CTG TCG TCG CTT AAT TGC TC-5′. Human DNA was positively validated by the housekeeping gene APC (5′-GTCCTTCACAGAATGAAA GATG-3′ and 3′-CTG CTT GAA GAA GAC ATA TGTTCG-5′). The size of the amplified fragments were, respectively, 399, 576, 360, 275, and 520 bp. Each amplification included a negative and positive control. Amplification reactions were carried out in 100 μL of reaction buffer containing 50 mM KCl, 2 mM $MgCl_2$, 10 mM Tris (pH 8.3), 200 μM each deoxynucleotide triphosphate, 2.5 units of Taq DNA polymerase (Perkin-Elmer-Cetus), 100 pmol of each primer, and 10 μL of proteinase K–digested sample. Samples were denatured at 95°C for 5 minutes, followed by 40 cycles of amplification (94°C for 1.5 minutes; annealing, 55°C for 2 minutes, with the exception of HPV-6/11 and APC, for which annealing was 40°C and 57°C, respectively; 72°C for 2 minutes; final extension, 7 minutes). Amplified products (15 μL) were electrophoresed through 1.6% agarose ethidium bromide-stained gels.

The HC2 test (Digene Corporation) uses probes for high-risk HPV types [16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68] and low-risk HPV types [6, 11, 42, 43, 44]. All HC2 tests were performed according with the manufacture's instructions and provided qualitative results (e.g., positive for high-risk HPV, positive for low-risk HPV, negative), since this methodology could not specify the different HPV genotypes.

Laser Treatment

All laser vaporizations were performed by a single surgeon in each center, and the same procedure was used throughout the centers. Patients underwent CO_2 laser vaporization (Coherent System 451 instrument, by Zeiss photocolposcopy attachment) with local anesthesia in an outpatient surgery setting.

Follow-up

Patients were followed-up with a vaginoscopy and Pap smear every 3 months for the first year and yearly thereafter, whereas HPV testing was performed yearly according to the methods provided in the "Methods" section. A vaginoscope-guided biopsy was performed in all suspicious areas. Follow-up of all the patients included in the present study was conducted for 5 years.

RESULTS

Patients

Sixteen of 33 patients who underwent neovagina reconstruction due to MRKH syndrome were treated according with the Vecchietti technique (48.5%), 16 patients were treated with a skin graft technique (48.5%), and one patient (3%) with a sigmoid interposition. The median age of the patients at vaginoplasty was 16.28 years (range, 15–19 years). The median time from the vaginal reconstruction to our referral was 8 years (range, 3–13 years), and the median age at our referral control was 23.14 years (range, 20–31 years).

All women were sexually active, and the age of their first sexual intercourse ranged between 16 and 24 years. The number of sexual partners was two or fewer in 26 of 33 patients (78.8%) and more than two in seven patients (21.2 %). Only three patients (9.0%) stated that they used condoms.

The culture of the vaginal swabs disclosed mycetes in three patients (9%), *Gardnerella vaginalis* in eight patients (24.2%), *Trichomonas vaginalis* in five patients (15.1%), chlamydia in three patients (9.0%), *Streptococcus agalactiae* in three patients (9.0%), and a coinfection by Trichomonas and Gardnerella in three patients (9.0%); these patients were treated with appropriate therapy according with the culture's findings. Vaginal pH evaluation ranged from 4.4 to 5.3.

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