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RADICAL VAGINAL TRACHELECTOMY WITH FERTILITY PRESERVATION IN EARLY STAGES OF UTERINE CERVICAL CANCER

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ABSTRACT

Background: Radical vaginal Trachelectomy (RVT) plays an important role as the definitive treatment of uterine cervical cancer.

Objective: To determine the conservative fertility in females in early pregnancy with invasive uterine cervical cancer stage IB1.

Patients and Methods: A prospective case-controls study was performed in cervical cancer IB1 stage who wished to preserve fertility. The patients underwent RVT and laparoscopic lymphadenectomy.

Results: Two study groups were formed: Pregnant and non-pregnant females. Nine non-pregnant patients were included. Epidermoid carcinoma was the histological type in 8, and one adenocarcinoma. Three patients presented lymph vascular invasion. The 17.4 lymph nodes obtained were negative for metastasis. The margins were free of lesion in the final histopathology report. Two pregnant patients were included. The average gestational age was 10.5 weeks, adenocarcinoma was the predominant histological type, without lymphovascular invasion. The 16.5 lymph nodes negative for metastasis were obtained, the margins were lesion free in the final histopathology report. Three live births were achieved. The average gestational age was 32.3 weeks, the weight was 2,055 g and the APGAR scores were 7.3-9.

Conclusions: It is possible to preserve fertility in much selected cases in early invasive uterine cervical cancer subjected to RVT.

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INTRODUCTION

Uterine cervical cancer continues to be an important health problem in developing countries. In Mexican women the uterine cervical cancer is the second cause of death due to cancer. Uterine cervical cancer is the seventh cause of cancer in developed nations (Arbyn, 2004). Brazil, Mexico, India and China together contribute 41% (n=216998) of new patients diagnosed and 42% (n=110186) of deaths by uterine cervical cancer. (Torre, 2015).

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Years of life adjusted for estimated incapacity due to uterine cancer in 2008 were 316 per 100,000 women per year in Mexico. (Serrano B, 2014). Due to the increased incidence of cancer in young females and the delay in fertility, new treatments for oncological management that favor the feasibility of conserving fertility as a viable option, have been designed. (Levine J, 2010). The corner-stone of uterine cervical cancer treatment in the early stages is radical hysterectomy with pelvic lymphadenectomy; (Kostov I, 2013) however, in 1994 Mathevet, P. Dargent, D. Roy, M. Beau, G., described the radical vaginal Trachelectomy (RVT) with pelvic laparoscopic lymphadenectomy for young females with early uterine cervical cancer who wished to preserve fertility.

The RVT is a viable and safe procedure that is feasible in the hands of Gynecologist Oncologists familiar with the technique, since it requires skill in surgical laparoscopy and vaginal surgery. (Shepherd JH, 2008) Advances in minimally invasive surgery have demonstrated the benefits of RVT that include: shorter hospital stay, less blood loss, less need for analgesics in the post-operative period, decrease in the rate of blood transfusions, decrease in the rate of complications, quicker recovery of the physiological functions, and improved aesthetic results (Frumovitz M, 2007). In fact, RVT is the elected surgical procedure in terms of preservation of the uterus, survival and gestational success (Park J, 2013).

Because uterine cervical cancer is second in frequency during pregnancy. Treatment in gestation should be focused on four main criteria: a) the grade of local dissemination (Stage and size of tumor), b) lymph node *status*, c) the term of the pregnancy, and, d) the histological type. In the first and second trimesters of pregnancy, magnetic resonance and laparoscopic lymphadenectomy are useful in deciding for conservative treatment (Morice P, 2012). Laparoscopic lymphadenectomy is a safe procedure during pregnancy for both mother and child, and lymphatic assessment is crucial to decide if the pregnancy can safely continue. The most important predictive factor to take into consideration is the presence of metastatic lymph nodes. The poor prognosis of patients with lymph node metastasis should be considered when deciding which criteria to follow (Chvatal R, 2013). The objective of the study was to determine the conservative fertility in females in early pregnancy with invasive uterine cervical cancer stage IB1.

MATERIALS AND METHODS

A prospective case-control study was performed in females with uterine cervical cancer stage IB1 who were subjected to RVT and laparoscopic lymphadenectomy (Dargent D, 2000) from 2009-2016. The surgical procedure was performed by the Gynecology Oncology Service at the Hospital of Gynecology and Obstetrics of the Sub-specialty Medical Unit at the National Occidental Medical Centre of the Mexican Social Security Institute (*Unidad Médica de Alta Especialidad, del Centro Médico Nacional de Occidente del Instituto Mexicano del Seguro Social*). The diagnosis was made by electro-surgical excision with a diathermic wire known as the Loop Electrosurgical Excision Procedure (LEEP), using the equipment ERBE ICC 200, manufactured by ERBE Elektromedizin GmbH Tübingen, Alemania®. (Santesso N, 2015) Also, the biopsy was obtained by rigid colposcopy and through cold knife cone biopsy (Conization).

Included, were females <45 years of age with invasive uterine cervical cancer stage IB1, with or without lymphovascular invasion, without evidence of sterility, who wished to achieve pregnancy or in normal pregnancy at the time of diagnosis and who wished to conserve pregnancy; with any type of histology, except small cell carcinomas or sarcomas, that did not invade the cervical canal, and with lymph nodes that were negative in the intra-operative studies or in the final results. Excluded, were patients with infertility, with tumor >4cm, that had endocervical involvement, with positive lymph nodes in the intra-operative or final studies, and if the procedure was insufficient as a solitary treatment. (Chuang LT, 2008). Two study groups were formed: non-pregnant females and pregnant females, with uterine cervical cancer in stage IB1.

Surgical procedure

The surgical technique began with exploratory laparoscopy and continued with dissection and resection of the lymph nodes of the external iliac, interiliac (Up to the bifurcation of the iliac artery), and the common iliac chains. The obturator fossa was dissected, identifying and respecting the obturator vessels and nerve, and the obturator and deep parametrial lymph nodes were resected conserving the uterine artery. When the lymph nodes were, frozen and reported negative for metastasis, the RVT was performed. The surgical procedure began by taking the vagina approximately 1-2cm from the Douglas sacto resect the superior portion of the vagina; the recto-vaginal wall and the uterosacral ligament were dissected, and preparing the pararectal space. The dissection continued with the paracervical fascia, liberating the bladder until identifying the superficial portion of the anterior parametrial reflection, forming the paravesical space. It was dissected and the retractor was introduced on the pelvic wall. The anterior *parametrium* was palpated until identifying the 'click' that the ureter knee produces upon pressing it against the retractor. The ureter was freed from the paracolpos and the medial portion of the superficial anterior and *deepparametrium* was ligated with Vicryl 0. The lateral *parametrium* was dissected, clamped and cut in the mid-portion, sutured with Vicryl 1, and fixed to the angles of the vagina. Afterwards, the descending portion of the uterine artery was clamped, cut and ligated. The external cervical orifice was identified passing a Hegar type 4 dilator until the uterine *isthmus* was identified. The cervix was involved 5mm below the uterine *isthmus* and the piece was surgically extracted. When the cytology mark of the endocervical margin was reported as negative for malignancy, the permeable opening of the cervical orifice was verified and a circular band was placed with Ethibond 3. (Figure 1). Finally, the vaginoplasty was performed avoiding occlusion at the external cervical orifice (Saadi, 2015).

Ethical considerations

The study was performed in accordance with the principles of ethical research in humans as stipulated by the Declaration of Helsinki from the 64th General Assembly, Fortaleza, Brazil, in 2013. The Good Clinical Practice Guidelines were followed in agreement with the norms established by the General Health Law of Mexico (*Ley General de Salud*) Category III, for research in human beings. The study was approved by the Ethics and Research Committee of the National Occidental Medical Centre of the Mexican Social Security Institute (*Instituto Mexicano del Seguro Social*) (R-2009-1310-38). All the procedures were in agreement with those stipulated in the guidelines of the General Health Law in Health Research Matters, second edition, of the Ethical Aspects for Research in Human Beings, Chapter 1, and Article 17. Individual charts were created. Confidentiality, and being informed of laboratory values and the results of clinical and medical evaluations, were guaranteed. Patients signed the Informed Consent Form in the presence of witnesses and with their signatures.

RESULTS

Non-pregnant patients

There were 9 patients in stage IB1 with an average age of 32.7 years. The diagnosis of uterine cervical cancer was made with LEEP in 5 patients and 4 were diagnosed by rigid colposcopy.

Surgical and oncological results

All the patients were subjected to RVT with laparoscopic lymphadenectomy without complications. The size of the tumor was <2cm in 8 patients and 2.1cm in 1 patient. In 8 patients (88.8%) the histological type was epidermoid carcinoma, and 1 adenocarcinoma. Three patients presented with lymphovascular invasion. On average, 17.4 lymph nodes were obtained, and all were negative for metastasis. The parametrial, vaginal, and endocervical margins were found free of lesion in the final histopathology report. At the end of follow-up, the average length of time illness-free was 56.1 months with a range of follow-up from 12-90 months. (Table 1)

Pregnant patients

Two pregnant patients in stage IBI with an average age of 32.5 years were included. The average gestational age was 10.5 weeks (The first was 7 weeks and the second 14 weeks). The diagnosis of uterine cervical cancer was made by cold knife cone biopsy (by conisation) in the first patient and by rigid colposcopy the second patient.

Surgical and oncological results

All the patients underwent RVT with laparoscopic lymphadenectomy without complications. The size of the tumor was <2cm in 1 patient and 4cm in the other. The histological type was adenocarcinoma in both patients.

Table 1. Ca Cu in early stages without pregnancy

Number	Age (years)	Stage	Histological type	Lymphovascular permeation	Lymph Nodes (number)	Free Period of Disease (months)
6***	34.16	IBI	Epidermoid	(-)	17.16	56
2	29.5	IBI	Epidermoid	(+)	17	49
1	31	IBI	Adenocarcinoma	(+)	20	76
Ca Cu in early stages with pregnancy						
1*	29	IBI	Adenocarcinoma	(-)	15	82
1**	36	IBI(4 cm)	Adenocarcinoma	(-)	18	3

Table 1. PATIENTS WITH FERTILITY CAPACITY. The nine non-pregnant patients were in stage IBI with disease-free surgical margins. *Patient with 7-week pregnancy. Pregnancy continued until week 37. Male live product of 3,300 g was obtained, with apgar of 8-9. **Patient with 14 weeks' pregnancy, 4 cm borderline tumor. The pregnancy was interrupted at 28 weeks, male live product of 1165 g was obtained, apgar 7-9. The product died of pneumonia at 40 days of birth. ***Patient who achieved pregnancy 4 months after the oncological treatment, was obtained female alive product at 32 weeks of gestation, 1,700 g of weight and apgar of 7-9. The product and the mother survived.

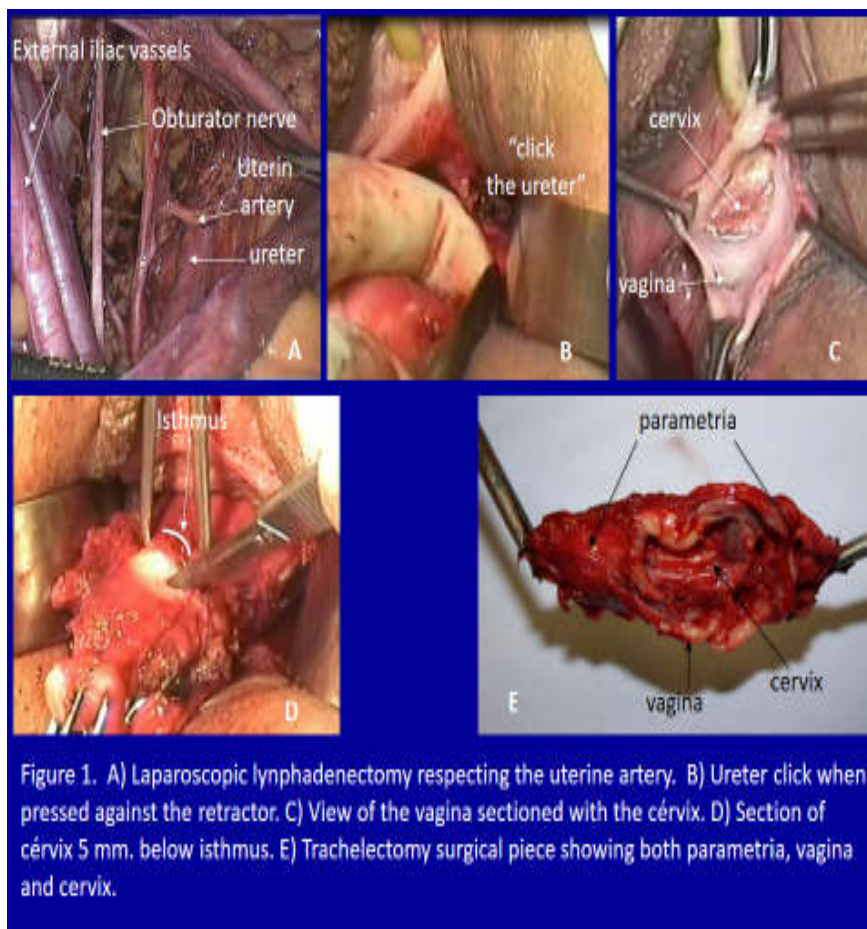


Figure 1. TRACHELECTOMY VAGINAL RADICAL. A) Laparoscopic lymphadenectomy respecting the uterine artery. B) Ureter "click" when pressed against the retractor. C) The vagina sectioned with the cervix. D) Section of cervix 5 mm below isthmus. E) Trachelectomy surgical piece showing both parametria, vagina and cervix

They did not present with lymphovascular invasion. On average, there were 16.5 lymph nodes obtained, all negative for metastasis. The parametrial, vaginal, and endocervical margins were free of lesion in the final histopathology report. The average length of time free of illness was 42.75 months with the first patient having 82 months' illness-free. The case of the second patient, due to her individual characteristics, was submitted to the Ethics Committee of the hospital to offer her neo-adjuvant treatment (Radiation-chemotherapy) due to the size of her tumor (4cm). Since the patient did not accept the neo-adjuvant treatment, RVT was performed with laparoscopic lymphadenectomy, obtaining 18 lymph nodes, all negative for metastasis, and with all the parametrial, vaginal, and endocervical margins free of lesions. The period free of illness was 3.5 months when tumor activity appeared in the cervical *isthmus* and it was necessary for her to undergo anatomical caesarean at 28 gestation weeks, and radiation-chemotherapy administration. Afterwards, she had a radical hysterectomy Piver III, finding residual uterine tumor of 1.5cm. Although the surgical margins were found free of lesions, she survived 6 months. The baby died due to pneumonia forty days after birth. (Table 1)

Obstetrical and neonatal results

Three live births were achieved: 2 from patients already pregnant and 1 from another patient who became pregnant 4 months after RVT. All live births occurred by caesarean. The average gestational age was 32.3 weeks. The average weight was 2,055g and the APGAR scores were 7.3-9. One live birth occurred at term (37 weeks) and two were premature at 32 and 28 weeks. The other two babies are currently alive and healthy (Table 1).

DISCUSSION

Women have delayed maternity due to changes in society and the economy, as well as some customs in different countries that have changed in recent decades. (Bunting I, 2007) The wave of development in which we find ourselves is one of the reasons why present-day women dedicate themselves to professional preparation, to sustain work activity and defer maternity. (Bunting, 2007) On the other hand, the advent of colposcopy clinics hassled to the increase in diagnoses of uterine cervical cancer at earlier stages, and health campaigns stimulate the pregnant population to have adequate prenatal care to reduce maternal death and cancer associated to pregnancy. (Boutas, 2014) In patients with early invasive uterine cervical cancer and the desire to preserve fertility, as well as those with uterine cervical cancer in the first trimester of pregnancy, RVT has been designed to preserve fertility and pregnancy (Gunasheelas, 2014). The RVT is a safe and viable option for treatment in highly select women with the diagnosis of early uterine cervical cancer who wish to preserve their fertility. It's appropriate to state that the oncological result of RVT is like radical abdominal hysterectomy in select cases. (Dargent, 2000). Regarding the different approaches for conservative treatment, the data that compare RVT to radical abdominal Traquelectomy are not sufficient to determine which surgical *focus* is superior. However, in our experience, we prefer the vaginal approach because laparotomy increases the adherence syndrome (Ditto 2015). We consider that there is no difference in the way to make the diagnosis, or in other words, in the use of conization with LEEP, cold knife or biopsy guided by colposcopy (Koeneman, 2016). As previously

demonstrated, the oncological results are directly proportional to the tumor size and histology (Schwarz TM, 2015). In our study, 75% of the tumors were epidermoid and 25% adenocarcinoma, and the management criteria was the same since all the adenocarcinomas were in stage IB1. The tumor size had negative repercussions on the results, since the patient with the 4cm tumor presented with disease progression, decreased survival, and prematurity that precipitated the death of the conception product compared to the patients with tumors <2 cm who evolved free of illness. The presence of lymphovascular invasion in three patients (Two with epidermoid and one with adenocarcinoma) did not have repercussions on the oncology results since they are currently illness-free. However, it should be considered, as the literature suggests, that it is still an adverse factor under discussion and for that reason patient follow-up should be close (Khunamornpong, 2013). Conization is a viable option for patients with uterine cervical cancer in stage IA1 as it has been previously reported (Filho Ch, 2015).

Nevertheless, more studies are required which demonstrate that less radical surgery with pelvic lymphadenectomy can be a management alternative for patients in stage IA2 and IB1 who have favorable tumor size and pathology characteristics; demonstrating that the *parametrium* is normal by being able to measure its thickness and determine the possibility of it being affected before surgery, for the correct selection of patients who would likely benefit from resection of the *parametrium*; which would reduce intra-operative morbidity and the obstetrical risks without sacrificing the oncology results (Karimi-Zarchi, 2013). Conservative management in invasive uterine cervical cancer is associated with good oncological results, preserving reproductive function, yet more prospective and larger studies are required that guarantee patient safety. (Naleway, 2015) In our study, we could not perform a global survival analysis due to the small number of patients, although the maximum follow-up of the illness-free period was almost 90 months. With respect to fertility, it's possible to achieve progress of pregnancies and conception after RVT. (Singh, 2015). It must also be considered that RVT is not innocuous and has complications that include: chronic vaginal discharge, abnormal uterine bleeding, dysmenorrhea, inflammation and ulcers caused by the band, amenorrhea, cervical stenosis, and complications in subsequent pregnancy. Traquelectomy can also lead to miscarriage in the second trimester of pregnancy, and to premature delivery. It is always recommended to deliver the product of conception by caesarean (Lee, 2006). The fact remains, and should be considered, that RVT is a surgical procedure with relative risk for miscarriage and infertility; but, it does make it possible for some patients to give birth to normal infants, with an acceptable low rate of recurrence, as found in our study where 66% of the infants were live births, and there was a rate of recurrence of 9%.

While in 2013 it was reported that the patients subjected to radical abdominal Traquelectomy obtain better oncological results, their results on fertility were unfavorable compared to RVT (Cao, 2013). The tumor size should be emphasized as an indication for RVT to improve results of fertility and the oncological prognosis (Cao T, 2015). The primary obstetrical complication in these types of patients continues to be premature labor, for which it is suggested that patients should be closely watched like a high-risk pregnancy (Singh, 2015). We conclude that RVT with laparoscopic lymphadenectomy in early invasive uterine cervical cancer seems to offer the same

good oncological and survival results as radical abdominal hysterectomy. The laparoscopic approach is safe and facilitates lymphadenectomy in reducing the processes of adhesions, with high potential to preserve fertility and bring the product of conception to term in pregnant women.

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