



Universiteit
Leiden
The Netherlands

Early stage cervical cancer : quality of cancer care and quality of life

Pieterse, Q.D.

Citation

Pieterse, Q. D. (2007, September 13). *Early stage cervical cancer : quality of cancer care and quality of life*. Retrieved from <https://hdl.handle.net/1887/12312>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/12312>

Note: To cite this publication please use the final published version (if applicable).

Chapter 7

Vaginal blood flow after radical hysterectomy with and without nerve-sparing. A preliminary report.

Q.D. Pieterse¹, M.M. ter Kuile¹, M.C. DeRuiter², J.B.M.Z. Trimbos¹, G.G. Kenter¹, C.P. Maas¹.

¹ Dept. of Gynaecology, Leiden University Medical Centre, Leiden, the Netherlands

² Dept. of Anatomy and Embryology, Leiden University Medical Centre, Leiden, the Netherlands

Int J Gynecol Cancer 2007; in press

Abstract

Objective: Radical hysterectomy with pelvic lymphadenectomy (RHL) for cervical cancer causes damage to the autonomic nerves which are responsible for increased vaginal blood flow during sexual arousal. The aim of the study of which we now report preliminary data was to determine whether a nerve-sparing technique leads to an objectively less disturbed vaginal blood flow response during sexual stimulation.

Methods: Photoplethysmographic assessment of vaginal pulse amplitude (VPA) during sexual stimulation by erotic films was performed. Subjective sexual arousal was assessed after each stimulus. Thirteen women after conventional RHL, 10 women after nerve-sparing RHL and 14 healthy premenopausal women participated. Data were collected between January and August 2006. The main outcome measure was the logarithmically transformed mean VPA. To detect statistically significant differences in mean VPA levels between the three groups, a univariate analysis of variance was used.

Results: Mean VPA differed between the three groups ($p = 0.014$). The conventional group had a lower vaginal blood flow response than the control group ($p = 0.016$), which tended also to be lower than that of the nerve-sparing group ($p = 0.097$). These differences were critically dependent on baseline vaginal blood flow differences between the groups. The conventional group follows a vaginal blood flow pattern similar to postmenopausal women.

Conclusions: Conventional RHL is associated with an overall disturbed vaginal blood flow response compared to healthy controls. Since it is not observed to the same extent after nerve-sparing RHL, it seems that the nerve-sparing technique leads to a better overall vaginal blood flow caused by less denervation of the vagina.

Introduction

Women with a history of radical hysterectomy with pelvic lymphadenectomy for cervical cancer (RHL) report a decrease in sexual interest, vaginal lubrication and genital swelling, which compromises sexual activity and results in considerable distress (1-4). Surgical damage to the pelvic autonomic nerves is responsible for a considerable part of the morbidity following radical hysterectomy (5-7). During radical hysterectomy the nerve supply to the blood vessels of the vaginal wall that is responsible for the neural control of the lubrication response is disrupted (1;4;5;8).

Psychophysiological assessment using photoplethysmographic vaginal pulse amplitude has been proven to be reliable in assessing the increase in vaginal blood flow during sexual arousal (9-11). The increased vaginal blood flow reflects a highly automated genital response mechanism, occurring irrespectively of subjective appreciation of the sexual stimulus (12;13). The genital physiological response is an involuntary reflex mediated by the (unconscious) autonomic nervous system (14;15). Maas et al. performed a study in which vaginal pulse amplitude during sexual stimulation by erotic films was assessed in women with a history of conventional RHL, women with a history of simple abdominal hysterectomy and in age-matched healthy controls. The results of the study indicated that conventional RHL is associated with a disturbed vaginal blood flow response during sexual arousal. The disturbed response could not be explained solely by uterus extirpation, since it was not observed to the same extent after simple hysterectomy. The difference in outcome might be related to a more extended denervation of the vagina with increasing radicality of surgery (10). A surgical technique in which the autonomic nerves are identified and subsequently preserved during surgery was developed at the Leiden University Medical Centre (LUMC) (6). The technique involved three steps: first, the identification and preservation of the hypogastric nerve in a loose tissue sheath underneath the ureter and lateral to the sacrouterine ligaments; second, the inferior hypogastric plexus in the parametrium is lateralized and avoided during parametrial transsection; third, the most distal part of the inferior hypogastric plexus is preserved during the dissection of the posterior part of the vesico-uterine ligament.

The aim of the study of which we now report preliminary data was to determine whether the nerve-sparing technique indeed leads to an objectively less disturbed vaginal blood flow response during sexual stimulation. Genital arousal was assessed by a photoplethysmograph, during sexual stimulation by erotic film in women with a history of a conventional RHL, in women with a history of a nerve-sparing RHL and in healthy premenopausal women. Subjective sexual arousal was assessed after each stimulus and self-report questionnaires were used to assess sexual functioning.

Patients and Methods

Study group

Since 2000 we perform the nerve-sparing modification of the RHL. Patients were recruited by reviewing medical files, collected prospectively in a database, of 156 women who had consecutively undergone a conventional RHL and 70 women who had undergone a nerve-sparing RHL for the treatment of cervical cancer stage I-IIa at the LUMC. In all cases a RHL type III was performed (16). None of the patients had participated in the study of Maas et al. (10). All patients in the study were treated by the same team of gynaecologic oncologists. Surgery had to have been at least one year before entry in the current study. Exclusion criteria for the current study were: a history of adjuvant radiotherapy or chemotherapy or signs of recurrent or metastatic cervical cancer; a history of bilateral oophorectomy; other perineal or abdominal surgery; post- or perimenopausal status. The hormonal status of the patients was assessed through history-taking evaluating vasomotor symptoms, hormonal cycles and age. If there was any doubt, the patient was classified as postmenopausal. Twenty three out of 156 (15%) patients in the conventional RHL group participated. Ten of these 23 patients were postmenopausal and were excluded from the analysis. Participation was refused for various reasons: no interest because of a lack of sexual problems (30), lack of time (26), intrusive nature of the experiment (36), or no reason given (41).

In the nerve-sparing RHL group, 11 out of 70 (16%) patients participated. One of the 11 patients was postmenopausal and was excluded from the analysis. Participation was refused for similar reasons: no interest because of a lack of sexual problems (6), lack of time (10), intrusive nature of the experiment (18), or no reason given (25).

Premenopausal women without sexual problems and without a history of abdominal or pelvic surgery or radiotherapy/ chemotherapy were recruited from the general population. Women contacted the investigators after reading an advertisement in a local paper. The exclusion criteria were checked through a semi structured clinical interview. None of the 14 recruited healthy controls had ever participated in research on sexual arousal.

Material and Response Measurements

All the interviews and experiments were carried out by one female doctor (Q.D.P). The assessor was not blinded for patients operation. Informed consent was obtained. All women received travelling expenses. The study was approved by the local Medical Ethics Committee.

Stimulus material identical to the study of Maas et al.(10) was used; all the subjects were exposed to an experimental session, that contained two 5 minutes neutral stimuli (during which a non-erotic documentary film excerpt was shown), and two erotic 5.5 minutes stimuli (erotic films depicting cunnilingus and intercourse). The erotic film excerpts were taken from so-called women-made, female-initiated, and female-centred erotic film (12).

Genital sexual arousal

The physiological evaluation of the genital response was carried out using vaginal photoplethysmography. The plethysmograph is a menstrual tampon-sized device containing a light-emitting diode and a phototransistor to detect light. The light source illuminates the capillary bed of the vaginal wall and the phototransistor responds to light reflected by the vaginal wall and the blood circulating within it. When the signal is connected to an alternating current (AC) amplifier, vaginal pulse amplitude (VPA) is measured, which reflects the phasic changes in vaginal engorgement accompanying each heart beat, with larger amplitudes reflecting higher levels of vaginal blood flow. Vaginal pulse amplitude (VPA) is currently the most sensitive, specific, and reliable measure of vaginal vasocongestion (9) and is used in earlier /other studies (17;18) on sexual function in women with neurological damage

Subjective sexual arousal

Subjective sexual arousal was assessed through self-reported ratings of sexual arousal that were collected after the two neutral stimuli and the two erotic stimuli. Subjects were asked to assess on a seven-point Likert scale (19) their feeling of sexual arousal. Each point of the Likert scale was described by a verbal label: 1 representing “not sexually aroused at all” to 7 “very strongly sexually aroused”.

Assessment of sexual and psychological functioning

The Gynecologic Leiden Questionnaire (LQ) is a 21 item measure, which is the first Dutch list consisting of items for sexual function, voiding- and bowel problems for women with cancer. This questionnaire is currently being validated. This self-report questionnaire is validated in a Dutch population of patients with early stage cervical cancer (20).

The Dutch version of the Female Sexual Function Index (FSFI) (21;22) is a 19 items self-report measure of female sexual function that assess sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The total FSFI score is an indication for sexual function.

The Dutch version of the Hospital Anxiety and Depression Scale (HADS) is a 14 items self-report measure to assess anxiety (7 items) and depression (7 items) (23;24), was used to assess the level of anxiety and depression.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) Dutch version 3.0 (25) is a 30 items self-report measure for assessing health-related quality of life of cancer patients. Only the global health status / quality of life scale (two items), was used for the current study.

The questionnaires were completed before the experiment.

Data reduction and analysis

The VPA was continuously recorded. VPA was sampled at 20 Hz across baseline and subsequent trials. A two-pass algorithm for automatic artefact removal (Molenkamp Technical Support Group, University of Amsterdam) was used to analyse the VPA data. After artefact deletion peak-to-trough amplitude was calculated for each remaining pulse and averaged over 60 second epochs.

Statistical calculations were performed with SPSS for Windows version 12. Prior to analysis, all dependent variables were examined for fit between their distributions and the assumptions of univariate analyses. To reduce the positive skewness of the VPA data, all VPA data were logarithmically transformed ($\log_{10}$). For each stimulus (two neutral stimuli and two erotic stimuli), a $\log_{10}$ VPA mean score was calculated by averaging all epochs of the specific stimulus. To analyse differences in the $\log_{10}$ VPA scores between three groups for the four stimuli, the $\log_{10}$ VPA mean scores were submitted to 3 (group) $\times$ 4 (stimulus) repeated measures ANOVA. Furthermore, to control for baseline differences, the $\log_{10}$ VPA mean scores were also submitted to 3 (group) $\times$ 3 (stimulus) repeated measures ANCOVA, using each individual's $\log_{10}$ mean baseline score of the first neutral stimulus as covariate. Following significant F ratios for each dependent measure, univariate post hoc analyses (multiple comparisons between all pairs of possible means) were performed to test specific stimulus effects. To analyse differences in the subjective sexual arousal between the three groups for the four stimuli, the mean subjective arousal scores were submitted to 3 (group) $\times$ 4 (stimulus) repeated measures ANOVA. To assess differences in subject's characteristics and dependent variables between the three groups, one-way analyses of variance or chi-square tests were used.

We were interested in a difference between the group of women with a nerve-sparing RHL and the group of women with a conventional RHL with a large size effect of at least $d=0.8$.

With an alpha value of 0.05, a power of 80% and an effect size of $d=0.8$, a number of minimal 26 women for each group is needed (26). We did not succeed to recruit this number of subjects for each group and it will take at least 3 years to collect enough subjects for this experiment. The results of the completed study will be reported later. In this preliminary report, with an alpha value of 0.05 and with the smallest number of ten patients in the nerve-sparing group and 13 patients in the conventional group, the power was 39 % to detect a difference with a large effect size between the two groups. Statistical significance was assigned at a level of $p<0.05$.

Results

Differences in biographical, medical status and psychological variables

Table 1 shows characteristics and outcome of the questionnaires of the 37 women included. None of the women used hormone replacement therapy. The women in the nerve-sparing RHL group were younger than the women in the conventional RHL and control group. In the conventional RHL group

Characteristics/ Questionnaires	Controls (n=14)	Conventional RHL (n=13)	Nerve-sparing RHL (n=10)	F/Chi-Square*	p-value
Age (y)	46.9±5.9	46.7±5.5	40.1±6.3	F=4.78	0.015
Operation-experiment(m)	-	107.7±41.1	25.6±18.4	F=34.28	0.000
Gynaecologic LQ					
Marital status					
With partner	8(57)	10(77)	7(70)	$\chi^2=1.24$	0.538
Without partner	6(43)	3(23)	3(30)		
Bladder dysfunction					
Incontinence complaints	6(43)	5(42)	6(60)	$\chi^2=0.91$	0.634
Bowel dysfunction					
Constipation complaints	0	7(45)	5(50)	$\chi^2=10.85$	0.004
Sexual dysfunction					
Not sexually active	4(29)	4(31)	3(30)	$\chi^2=0.02$	0.992
FSFI					
Desire	5.8±0.7	6.1±1.9	4.9±1.9	F=1.21	0.318
Arousal	15.8±1.4	12.5±6.2	10.7±6.0	F=2.02	0.156
Lubrication	17.3±3.2	17.1±6.2	14.9±7.5	F=0.40	0.676
Orgasm	12.8±2.1	10.8±5.2	9.6±5.6	F=0.93	0.409
Satisfaction	12.9±1.5	9.5±4.5	9.3±4.5	F=2.23	0.131
Pain	12.6±3.9	11.7±6.2	11.6±5.6	F=0.09	0.914
Total FSFI	77.1±5.7	67.7±24.8	60.9±29.1	F=1.03	0.375
HADS					
Anxiety	7.3±1.8	6.6±3.2	9.6±7.1	F=1.00	0.386
Depression	6.4±1.8	8.3±4.5	8.9±5.2	F=0.81	0.456
EORTC QLQ-C30					
Global health status	6.4±0.7	5.2±1.2	5.1±1.2	F=6.49	0.004

Tabel 1. Patients characteristics and outcome of the questionnaires. SD, standard deviation; RHL, radical hysterectomy with pelvic lymphadenectomy; y, years; m, months; LQ, Leiden Questionnaire; FSFI, Female Sexual Function Index (A higher score means a better sexual function); HADS, Hospital Anxiety and Depression Scale (A higher score means more complaints of anxiety or depression). EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (A higher score means a better global health status) *Observed two-tailed significance. Statistical significance at a level of $p < 0.05$. Data are presented as mean $\pm$ SD or n (%), unless otherwise indicated.

the time-interval between the operation and the experiment was three times as long as that of the nerve-sparing RHL group. Constipation complaints were more frequently reported by the conventional RHL and nerve-sparing RHL group compared to the controls. No differences were found for sexual and bladder dysfunction.

Differences in genital arousal

Figure 1 shows VPA responses in the three subjects groups throughout the whole experimental session. The VPA mean scores differed between the three groups ($F(2, 34) = 4.84$, $p = 0.014$); the conventional RHL group had overall, significantly lower VPA mean scores than the control group ($p = 0.016$). The VPA mean scores of the conventional group tended also to be lower than the VPA mean scores of

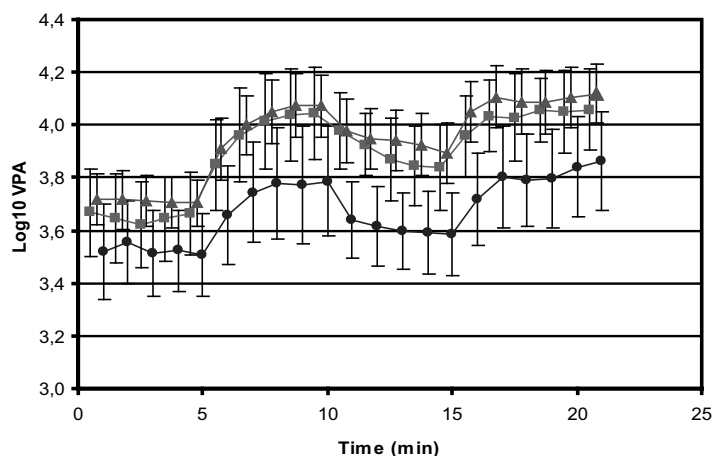


Figure 1. Change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).

—●—=Conventional RHL (n=13), —■—=Nerve-sparing RHL (n=10), —▲—=Controls (n=14). RHL, radical hysterectomy with pelvic lymphadenectomy. See colour figure page 153.

the nerve-sparing group ($p=0.097$). No differences were found between the control group and the nerve-sparing group ($p=1.000$). These results indicate that the VPA responses in the conventional RHL group were significantly lower throughout the whole experimental session. Moreover, the two erotic films were equally effective in enhancing genital arousal in the three groups which was reflected by significantly higher VPA mean scores of the two erotic stimuli compared to the mean VPA scores of the two neutral stimuli ($F(3, 102)=66.40$, $p<0.001$). Table 2 shows the untransformed VPA mean scores for the three groups and four stimuli.

As the conventional RHL group had significantly lower baseline VPA scores than the controls, we repeated the analysis while controlling for individual baseline differences. After controlling, the VPA responses in the three subject groups throughout the experimental session were comparable ($p=0.140$). This indicates that the differences in levels throughout the experimental session between the three subject groups were critically dependent on the baseline VPA scores (Fig. 1).

Because the women in the nerve-sparing group were significantly younger than the women in the other two groups and the time-interval between the operation and the experiment was longer for the conventional group, we performed the same analyses for VPA mean scores while controlling for age or time-interval between operation and experiment. After controlling for age or time interval the outcome did not change. These results indicate that the VPA responses throughout the whole experimental session are not affected by age or time-interval.

	Controls (n=14)	Conventional RHL (n=13)	Nerve-sparing RHL (n=10)
Objective report: vaginal pulse amplitude (mV)			
Neutral stimulus 1	1.8±1.0	1.2±0.7	1.7±1.0
Erotic stimulus 1	3.8±2.0	2.3±1.7	3.8±2.3
Neutral stimulus 2	3.1±1.6	1.5±0.7	2.9±1.6
Erotic stimulus 2	4.5±2.4	2.5±1.8	4.0±2.5
Subjective report: sexual arousal (Likert scale)			
Neutral stimulus 1	1.6±0.4	1.2±0.6	1.2±1.1
Erotic stimulus 1	3.6±1.6	3.2±1.2	3.3±1.1
Neutral stimulus 2	1.2±0.6	1.5±0.7	1.3±0.5
Erotic stimulus 2	4.4±1.5	4.2±1.4	3.7±1.4

Table 2. The mean and SD of the untransformed VPA mean scores in millivolt for the three groups and the mean and SD of the mean subjective arousal scores during the four stimuli. SD, standard deviation; VPA, Vaginal Pulse Amplitude; mV, millivolt. Data are presented as mean ± SD.

Differences in subjective arousal

The mean score on subjective arousal was significantly higher during erotic stimulus 1 and 2 compared to neutral stimulus 1 and 2 ($F(3, 102) = 108.36, p < 0.001$). The three subject groups reported the same level of subjective sexual arousal. These results indicate that the erotic films were equally effective in enhancing subjective sexual arousal in the three groups. Table 2 shows the mean subjective arousal scores of the three groups and four stimuli.

Differences in postmenopausal and premenopausal status, post-hoc analyses

Literature data show that postmenopausal women have a significantly lower baseline vaginal blood flow compared to premenopausal women (10;27;28). To explore the hypothesis that the vaginal blood flow response of the conventional RHL group follows a pattern comparable with that of postmenopausal women, we used our data of the postmenopausal controls (n=12) and postmenopausal women with a history of a conventional RHL (n=10) who were excluded from the earlier main analyses. These postmenopausal women met all the other inclusion criteria of our study.

Figure 2 shows the VPA responses in four different groups; post- and premenopausal controls and post- and premenopausal patients with a history of conventional RHL. Visual inspection of the data indicates that the premenopausal women of the conventional RHL group follow a pattern comparable with that of postmenopausal women. We subsequently performed statistical analyses to quantify the differences in VPA responses. A two subject groups (conventional vs controls) by hormonal status (premenopausal vs postmenopausal) by the four stimuli analysis revealed that the conventional RHL groups had overall lower VPA scores ($p=0.022$). Furthermore a trend for the interaction effect between group and hormonal status in VPA responses ($F(1, 45) = 2.87, p = 0.097$) was found. Post hoc analyses showed a significantly higher VPA response for the premenopausal controls compared to the premenopausal women with a history of conventional RHL ($p=0.024$), confirming the visual impression.

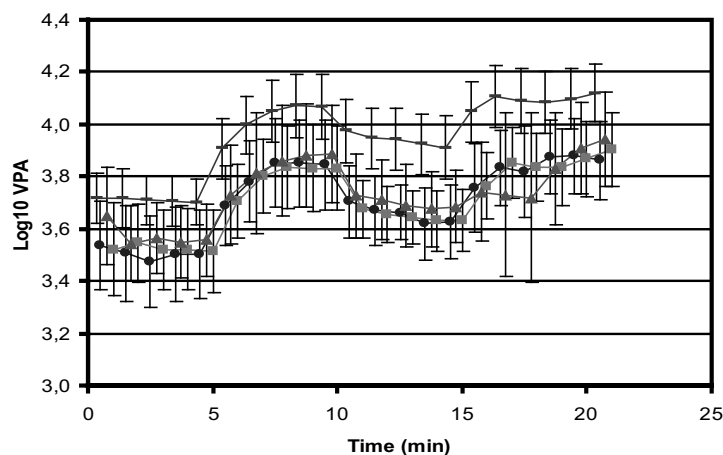


Figure 2. Postmenopausal versus premenopausal; change in logarithmically transformed mean vaginal pulse amplitude (log10VPA) during experimental session: Neutral stimulus 1 (Baseline assessment) (1-5 min), Erotic stimulus 1 (6-10 min), Neutral stimulus 2 (11-15 min), Erotic stimulus 2 (16-21 min).

—●—=Conventional RHL, postmenopausal (n=10), —■—=Conventional RHL, premenopausal (n=13), —▲—=Controls, postmenopausal (n=12), —=Controls, premenopausal (n=14) RHL, radical hysterectomy with pelvic lymphadenectomy. See colour figure page 153.

Discussion

This is the first study in which vaginal photoplethysmography was used to compare the functional results of a nerve-sparing modification of the RHL with the conventional RHL. Vaginal blood flow response during sexual stimulation was evaluated through objective assessment using photoplethysmography in women with a history of RHL, in women after nerve-sparing RHL and in healthy controls.

Although we did not yet succeed to recruit the number of subjects which we need according to our power calculation we decided to report preliminary data, because we feel that the results raise many interesting questions. The previous study from our group showed that damage to the autonomic nerves results in disrupted vaginal blood flow response during sexual stimulation. During sexual arousal a history of conventional RHL was associated with a significantly lower vaginal blood flow response compared to healthy controls (10). The results of the current study are partly in line with this; we also found that the conventional group had significantly lower VPA mean scores than the control group. The VPA mean scores of the conventional group tended also to be lower than the VPA mean scores of the nerve-sparing group. These differences in VPA were critically dependent on baseline differences between the three groups, and occurred despite the fact that these three groups felt an equally strong sexual arousal after the erotic stimulus condition. This implies that, in a non-stimulated situation,

patients with a history of conventional RHL probably have a lower vaginal blood flow than healthy controls and patients after a nerve-sparing RHL. Consequently, the vaginal blood flow during sexual stimulation does not reach the same high level in women with a history of conventional RHL.

The strength of the current study is the fact that all patients were treated by the same group of gynecologic oncologists, which ensures a uniform surgical technique.

The most ideal design would have been a pre-operative versus post-operative vaginal pulse amplitude assessment within subjects. We did not carry out such a study because we felt it was unethical to ask women in the period leading up to major cancer surgery to take part in an emotionally confronting psychophysiological sexual assessment.

In general, it has proven to be difficult to recruit women after they have had their treatment because of the intrusive nature of this experiment. For this reason it will take at least 3 years before we will have recruited a sufficient number of subjects for each group.

In interpreting the results of this preliminary analysis, the limits of the design and its size should be taken into account. The sample used was small. The fact that we did not find a significant difference between the conventional RHL group and the nerve-sparing RHL group could possibly be a consequence of relatively small power (39%) of the study so far (26).

Previous studies have shown that participants in sexuality studies tend to be more sexually liberal and permissive, and more sexually active than non-participants (29) which might influence the representativity of our sample. In the current study the control group showed mean FSFI total scores comparable with women without sexual problems (22). The two patients groups did not differ significantly from our control group. This could imply that women with more severe dysfunctions refrained from participating and that the difference in vaginal blood flow between the nerve-sparing RHL group and conventional RHL group might be an under-estimate.

The similarity of the VPA response curve of the women with a history of a conventional RHL and postmenopausal women is striking. In line with our findings, Laan et al.(27;30) also reported that postmenopausal women displayed significantly lower VPA responses than premenopausal women in the basal (unstimulated) state. They also found that the changes in VPA responses during erotic stimulation were similar in both premenopausal and postmenopausal women.

We suggest that a common pathophysiologic mechanism explaining the low basal vaginal blood flow in postmenopausal women and women with a history of conventional RHL could be an altered vascular smooth muscle contraction state in the vaginal blood vessels. We postulate that the observed altered vaginal blood flow in women with a history of a conventional RHL and postmenopausal women is in both cases the result of a reduced number of autonomic nerve fibres in the vascular smooth muscle cells in the vagina. Recent studies have shown both in animal models as well as in human tissue that the autonomic nerves which innervate the reproductive organs have been found to be responsive to circulating steroids such as oestrogen. These nerves express oestrogen receptor α (ER α) and oestrogen receptor β (ER β) (31-34). A changed number of autonomic nerve fibres in the vascular wall of

the vagina mediated by either direct nerve disruption (conventional RHL) or low oestrogen levels which modulate nerve density through oestrogen receptors in the vaginal wall (postmenopausal women) causes a changed contraction state of the vaginal arteries.

Chronic oestrogen exposure reduces the density of sympathetic nerves, but increases the density of parasympathetic nerves (31;32). Regarding vaginal blood flow, an increase of parasympathetic nerves would lead to vascular smooth muscle relaxation resulting in an increased VPA. This explains the higher baseline VPA in premenopausal women. Alternatively, a hypoestrogen status leads to a sympathetic hyperinnervation, causing vascular smooth muscle contraction resulting in a lower baseline VPA in postmenopausal women.

Interestingly, the typical sexual complaints reported by women with a history of conventional RHL (2-4) are similar to postmenopause-related sexual problems (35-37). These sexual complaints include dyspareunia, a dry vagina, reduced vaginal lubrication and a decline in sexual interest.

ER β , the receptor which is associated with human vaginal vascular smooth muscle has been documented to be expressed in the uterosacral ligaments (38). The critical modification of the conventional RHL into a nerve-sparing technique is the alternative surgical dissection of the uterosacral ligaments which contain essential parts of the pelvic autonomic nerves (6). Sparing the autonomic nerves expressing ER β could explain the higher baseline VPA in the premenopausal women with a history of nerve-sparing RHL.

The physiological model behind the subsequent 'normal' increase in VPA once the subject (after conventional RHL or in postmenopausal state) is erotically stimulated, i.e. after a low baseline, the vaginal blood flow increases to the same extent as in healthy controls but never reaches the high flow of controls, is the endothelin/ Nitric oxide (NO) system. Vessel walls react to sheer stress caused by blood pressure changes. Endothelin release results in vasoconstriction, while NO induces vasodilatation. This ability of the arteries to adapt to changes in the circulation is not regulated by the autonomic nervous system. This explains why a partly denervated vagina does show a relatively normal vaginal blood flow response.

In conclusion, the preliminary data from the present study show that women with a history of nerve-sparing surgery seem to have an overall better vaginal blood flow. Further research of the functional results of nerve-sparing modifications of RHL should therefore be performed, to prove without any doubt that nerve-sparing techniques lead to lower sexual morbidity with similar treatment results.

Acknowledgements

We gratefully acknowledge P.H.C. Eilers (Ph.D.) from the Department of Statistics for his valuable advice on the statistical analysis. Furthermore, we want to thank C. Tuijnman (M.A.) for her practical explanation of the use of the plethysmography, B. Molenkamp and C. Kramer for technical support. The authors would also thank G.J. van Dijk (M.D., Ph.D.) for offering the possibility to perform this research project at the Department of Neurology.

References

- (1) Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. *Lancet* 2007; 369:512-525.
- (2) Pieterse QD, Maas CP, ter Kuile MM, Lowik M, van Eijkeren MA, Trimbos JB et al. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. *Int J Gynecol Cancer* 2006; 16:1119-1129.
- (3) Jensen PT, Groenvold M, Klee MC, Thranov I, Petersen MA, Machin D. Early-stage cervical carcinoma, radical hysterectomy, and sexual function. A longitudinal study. *Cancer* 2004; 100:97-106.
- (4) Bergmark K, Avall-Lundqvist E, Dickman PW, Henningssohn L, Steineck G. Vaginal changes and sexuality in women with a history of cervical cancer. *N Engl J Med* 1999; 340:1383-1389.
- (5) Butler-Manuel SA, BATTERY LD, A'Hern RP, Polak JM, Barton DP. Pelvic nerve plexus trauma at radical hysterectomy and simple hysterectomy: the nerve content of the uterine supporting ligaments. *Cancer* 2000; 89:834-841.
- (6) Trimbos JB, Maas CP, DeRuiter MC, Peters AA, Kenter GG. A nerve-sparing radical hysterectomy: guidelines and feasibility in Western patients. *Int J Gynecol Cancer* 2001; 11:180-186.
- (7) Hockel M, Horn LC, Fritsch H. Association between the mesenchymal compartment of uterovaginal organogenesis and local tumour spread in stage IB-IIIB cervical carcinoma: a prospective study. *Lancet Oncol* 2005; 6:751-756.
- (8) Levin RJ. The physiology of sexual function in women. *Clin Obstet Gynaecol* 1980; 7:213-252.
- (9) Laan E, Everaerd W, Evers A. Assessment of female sexual arousal: response specificity and construct validity. *Psychophysiology* 1995; 32:476-485.
- (10) Maas CP, ter Kuile MM, Laan E, Tuijnman CC, Weijnenborg PT, Trimbos JB et al. Objective assessment of sexual arousal in women with a history of hysterectomy. *BJOG* 2004; 111:456-462.
- (11) Sintchak G, Geer JH. A vaginal plethysmograph system. *Psychophysiology* 1975; 12:113-115.
- (12) Laan E, Everaerd W, van Bellen G, Hanewald G. Women's sexual and emotional responses to male- and female-produced erotica. *Arch Sex Behav* 1994; 23:153-169.
- (13) Meston CM. The psychophysiological assessment of female sexual function. *J Sex Educ Ther* 2000; 25:6-16.
- (14) Basson R. Rethinking low sexual desire in women. *BJOG* 2002; 109:357-363.
- (15) Laan E, Everaerd W. Determinants of female sexual arousal. *Psychophysiological theory and data. Annu Rev Sex Res* 1995; 6:32-76.
- (16) Piver MS, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. *Obstet Gynecol* 1974; 44:265-272.

- (17) Pras E, Wouda J, Willemse PH, Midden ME, Zwart M, de Vries EG et al. Pilot study of vaginal plethysmography in women treated with radiotherapy for gynecological cancer. *Gynecol Oncol* 2003; 91:540-546.
- (18) Sipski ML, Alexander CJ, Rosen RC. Physiological parameters associated with psychogenic sexual arousal in women with complete spinal cord injuries. *Arch Phys Med Rehabil* 1995; 76:811-818.
- (19) Likert R. A Technique for the Measurement of Attitudes. *Archives of Psychology* 1932; 101:40, 55.
- (20) Pieterse Q, Ter Kuile MM, Maas C, Kenter G. The Gynaecologic Leiden Questionnaire: psychometric properties of a self-report questionnaire of sexual function and vaginal changes for gynaecological cancer patients. Submitted 2007.
- (21) Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther* 2000; 26:191-208.
- (22) ter Kuile MM, Brauer M, Laan E. The Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS): psychometric properties within a Dutch population. *J Sex Marital Ther* 2006; 32:289-304.
- (23) Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67:361-370.
- (24) Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997; 27:363-370.
- (25) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85:365-376.
- (26) Cohen J. Statistical power analysis for the behavioral sciences. 2 ed. Hillsdale NJ: Lawrence Erlbaum, 1988.
- (27) Laan E, van Lunsen RH. Hormones and sexuality in postmenopausal women: a psychophysiological study. *J Psychosom Obstet Gynaecol* 1997; 18:126-133.
- (28) Meyers LS, Morokoff PJ. Physiological and subjective sexual arousal in pre-and postmenopausal women and postmenopausal women taking replacement therapy. *Psychophysiology* 1986; 23:283-292.
- (29) Morokoff PJ. Volunteer bias in the psychophysiological study of female sexuality. *J Sex Res* 1986; 22:35-51.
- (30) Laan E, van Lunsen RH, Everaerd W. The effects of tibolone on vaginal blood flow, sexual desire and arousability in postmenopausal women. *Climacteric* 2001; 4:28-41.

- (31) Papka RE, Mowa CN. Estrogen receptors in the spinal cord, sensory ganglia, and pelvic autonomic ganglia. *Int Rev Cytol* 2003; 231:91-127.
- (32) Zoubina EV, Smith PG. Sympathetic hyperinnervation of the uterus in the estrogen receptor alpha knock-out mouse. *Neuroscience* 2001; 103:237-244.
- (33) Gebhart JB, Rickard DJ, Barrett TJ, Lesnick TG, Webb MJ, Podratz KC et al. Expression of estrogen receptor isoforms alpha and beta messenger RNA in vaginal tissue of premenopausal and postmenopausal women. *Am J Obstet Gynecol* 2001; 185:1325-1330.
- (34) Fu X, Rezapour M, Wu X, Li L, Sjogren C, Ulmsten U. Expression of estrogen receptor-alpha and -beta in anterior vaginal walls of genuine stress incontinent women. *Int Urogynecol J Pelvic Floor Dysfunct* 2003; 14:276-281.
- (35) Dennerstein L, Dudley E, Burger H. Are changes in sexual functioning during midlife due to aging or menopause? *Fertil Steril* 2001; 76:456-460.
- (36) McCoy NL, Davidson JM. A longitudinal study of the effects of menopause on sexuality. *Maturitas* 1985; 7:203-210.
- (37) Dennerstein L, Smith AM, Morse CA, Burger HG. Sexuality and the menopause. *J Psychosom Obstet Gynaecol* 1994; 15:59-66.
- (38) Chen GD, Oliver RH, Leung BS, Lin LY, Yeh J. Estrogen receptor alpha and beta expression in the vaginal walls and uterosacral ligaments of premenopausal and postmenopausal women. *Fertil Steril* 1999; 71:1099-1102.

