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Frequency Domain Near-Infrared Spectroscopy of The Uterine Cervix During Cervical Ripening

Baños, A

Abstract: Objective: Preterm labor is a common obstetric complication. Clinical evaluation of cervical ripening to predict preterm labor has a substantial inter- and intraobserver variability. We used frequency domain near-infrared spectroscopy (FD-NIRS) to non-invasively investigate the changes of the optical properties (i.e., absorption and scattering of light) in the uterine cervix during druginduced cervical ripening. Methods: Ten volunteers scheduled for abortion were examined. Optical properties of the uterine cervix were measured and physiological parameters were calculated prior to and after induction of cervical ripening using topical misoprostol. Mean relative changes, standard error of the mean as well as statistical significance using the t-test were calculated for oxy- and deoxyhemoglobin, total hemoglobin, oxygen-saturation, and water. The wavelength-dependent decrease of scattering (scatter power) was calculated by an exponential fit and tested with the Wilcoxon test. Results: Misoprostol induced a decrease in total hemoglobin of 21+/-6% (P<0.05), a decrease in oxyhemoglobin of 22+/-6% (P<0.05), a decrease in deoxyhemoglobin of 16+/-11% and an increase of 368% (P<0.005) in water content. The scatter power was significantly lower (P<0.05) after cervical ripening. Conclusion: Our results show that FD-NIRS is a promising diagnostic tool to detect changes in cervical concentrations of hemoglobin and water. A severe tissue edema, probably due to a hormone-induced inflammatory process, seems to be important for cervical ripening. The reduction in total hemoglobin is likely to be a consequence of the increased water content of the tissue resulting in a dramatic increase of the distance between vessels. We propose this technology to assess the cervical ripening and eventually to predict preterm labor. Lasers Surg. Med. 39:641–646, 2007.

Universitätsspital Zürich
Departement für Frauenheilkunde
Vorsitzender: Prof. Dr. med. R. Zimmermann
Klinik für Gynäkologie
Direktor: Prof. Dr. med. D. Fink

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Frequency Domain Near-Infrared Spectroscopy of The Uterine Cervix During Cervical Ripening

Ana Baños, MD,[1]* Martin Wolf, PhD,[2] Claudia Grawe, MD,[1] Michèle Stahel, MD,[1] Daniel Haensse, PhD,[2] Daniel Fink, MD,[1] and René Hornung, MD[1]

[1]*Department of Obstetrics and Gynecology, University Hospital Zurich, Zurich, Switzerland*
[2]*Biomedical Optics Research Laboratory, Clinic of Neonatology, University Hospital Zurich, Zurich, Switzerland*

Objective: Preterm labor is a common obstetric complication. Clinical evaluation of cervical ripening to predict preterm labor has a substantial inter- and intraobserver variability. We used frequency domain near-infrared spectroscopy (FD-NIRS) to non-invasively investigate the changes of the optical properties (i.e., absorption and scattering of light) in the uterine cervix during drug-induced cervical ripening.
Methods: Ten volunteers scheduled for abortion were examined. Optical properties of the uterine cervix were measured and physiological parameters were calculated prior to and after induction of cervical ripening using topical misoprostol. Mean relative changes, ± standard error of the mean as well as statistical significance using the t-test were calculated for oxy- and deoxyhemoglobin, total hemoglobin, oxygen-saturation, and water. The wavelength-dependent decrease of scattering (scatter power) was calculated by an exponential fit and tested with the Wilcoxon test.
Results: Misoprostol induced a decrease in total hemoglobin of $21 \pm 6\%$ ($P < 0.05$), a decrease in oxyhemoglobin of $22 \pm 6\%$ ($P < 0.05$), a decrease in deoxyhemoglobin of $16 \pm 11\%$ and an increase of $36 \pm 8\%$ ($P < 0.005$) in water content. The scatter power was significantly lower ($P < 0.05$) after cervical ripening.
Conclusion: Our results show that FD-NIRS is a promising diagnostic tool to detect changes in cervical concentrations of hemoglobin and water. A severe tissue edema, probably due to a hormone-induced inflammatory process, seems to be important for cervical ripening. The reduction in total hemoglobin is likely to be a consequence of the increased water content of the tissue resulting in a dramatic increase of the distance between vessels. We propose this technology to assess the cervical ripening and eventually to predict preterm labor. Lasers Surg. Med. 39:641–646, 2007.   © 2007 Wiley-Liss, Inc.

Key words: frequency domain near-infrared spectroscopy; preterm labor; cervical ripening

INTRODUCTION

Preterm labor is responsible for 70% of perinatal mortality and nearly half of long-term neurological morbidity [1] and is probably one of the most challenging problems in modern obstetrics and gynecology. In the United States, more than one-half million infants were born preterm in 2004, a rate of 12,5% and the highest number reported since comparable national data on gestational age have been available (1981) [2]. One of the keys to treating preterm labor and preventing severe neonatal complications would be early identification of women at risk. This would allow the initiation of important interventions to delay delivery and to improve neonatal outcome. Clinical evaluation of cervical ripening to predict preterm labor has a substantial inter- and intraobserver variability and do not provide accurate diagnosis or prediction. Although excellent research has been performed to understand induction of spontaneous and preterm delivery, a more accurate method would be invaluable for the determination of cervical status and the diagnosis of preterm cervical ripening.

Cervical ripening may be induced by local infection, cervical incompetence, or uterine contractions. Undoubtedly, cervical ripening is associated with many biochemical and physiological changes of the cervical tissue. Changes in blood perfusion and water content may be reflected in changes in optical properties (i.e., absorption and scattering of light) of the uterine cervix during pregnancy and labor. However, non-invasive measurements of the optical properties in vivo have not been made so far in pregnant women.

Near-infrared diffuse reflectance spectroscopy (NIRS) is used to non-invasively characterize optical properties of thick tissues in vivo [3]. Optical properties can be quantitatively defined in terms of absorption and effective scattering parameters, μ_a and μ'_s, respectively. These parameters are sensitive to the tissue concentration of light-absorbing molecules and light scattering structures. The primary tissue contributors to light absorption are assumed to be oxy- and deoxyhemoglobin (O_2Hb, HHb), water (H_2O), lipids, cytochromes, and melanin [4]. Light scatterers are tissue structural elements, such as cellular

components and fibrous materials in the extracellular matrix (e.g., collagen/elastin).

The main limitation of NIRS was the inability to make quantitative measurements because of the difficulty to separately measure μ_a and μ'_s. Frequency domain near-infrared spectroscopy (FD-NIRS) is a NIRS technique capable of solving this problem and quantifying absolute tissue μ_a and μ'_s values and absolute concentrations of tissue O_2Hb, HHb, tHb (total hemoglobin), StO_2 (oxygen-saturation), and H_2O [5]. The instrumentation and theoretical background for FD-NIRS have been described elsewhere [6,7].

The present study is based on the hypothesis that optical properties of cervices change during the process of cervical ripening and that the quantification of the optical properties in vivo by means of FD-NIRS will provide an insight into physiology and pathology of cervices during cervical ripening.

We therefore use FD-NIRS technology to study the optical properties of the uterine cervix in patients undergoing drug-induced cervical ripening for abortion.

This appears to be the first clinical study which measures non-invasively and quantitatively the absorption and the scattering of light as well as the physiological properties of the uterine cervix during cervical ripening.

MATERIALS AND METHODS

The FD-NIRS instrument used at the Department of Obstetrics and Gynecology, University Hospital of Zurich, is a modified Imagent (ISS, Champaign, IL) and is shown in Figure 1. It is equipped with seven near infrared diode lasers (emitting at 690, 730, 750, 808, 870, 920, and 970 nm) and one avalanche photodiode light detector. The instrument includes a pair of frequency synthesizers (PTS 500 Frequency Synthesizer, Programmed Test Sources, Inc., Littleton, MA) working in the range of 130–490 MHz and capable of switching frequencies within less than 1 milliseconds. One frequency synthesizer modulates the intensity of the laser diodes, while the other modulates the detector at a frequency which is 5 kHz different from the source modulation, thus demodulating the light frequency at the detector. The instrument is equipped with a complete software package (Boxy, ISS) for data acquisition and two calibration blocks with known optical properties. Once data acquisition is initiated the frequency dependence of the photon density wave's phase and amplitude is measured in steps of 10 MHz and fit to analytically derived model functions in order to calculate μ_a and μ'_s parameters for each wavelength. In addition, the wavelength-dependence of absorption is automatically used to calculate O_2Hb, HHb, tHb, StO_2, and H_2O. The system is now fully automated and data acquisition time is approximately 40 seconds.

For the present study we manufactured a probe (inlet Fig. 1), similar to the previously described [8], specifically designed for measurements of the human uterine cervix. The vaginal probe was slightly bent allowing good visualization during placement on the cervix. Eight multimode silica fibers (400 µm diameter, 3 M FT 400 EMT, Thorlabs,

Fig. 1. The FD-NIRS instrument used for the present study is shown. The inlet shows the cervical probe specially manufactured for this study. [Figure can be viewed in color online via www.interscience.wiley.com.]

Inc., Newton, NJ) were coupled to the laser source to transmit the light to the tip of the probe. One glass fiber bundle (3 mm diameter) conducts the light from the tip of the probe to the detector. The source-detector separation is 10 mm. Condom-like latex-covers were used to prevent transfection from patient to patient. The latex cover did not affect light transmission as investigated in some pilot measurements (data not shown).

A total of 10 volunteers scheduled for technical abortion were included in the study after written informed consent was obtained. The study was approved by the local ethical committee under the protocol StV 19/2003.

Age was 31 ± 6 years (mean $\pm$ SD), eight patients were nulliparous, one patient primiparous (history of elective cesarean delivery), and one patient multiparous (history of two spontaneous deliveries more than 10 years ago).

All patients underwent a routine gynecological examination, a transvaginal sonography and paper work was done to follow legal requirements for abortion. The gestational age was 8 week's plus 6 ± 9 days (mean $\pm$ SD).

Optical properties of the uterine cervix were determined prior to and after induction of cervical ripening using misoprostol (Cytotec®, Pfizer, Switzerland), a synthetic prostaglandin E_1. One hundred micrograms Cytotec was applied intravaginally for at least 6 to no more than 10 hours following the application of Cytotec in the operation room immediately prior to the surgical

procedure. Postinduction measurements were performed in the operating room immediately prior to the surgical procedure.

The uterine cervix was cleaned using a dry cotton swab to remove mucous and detritus in order to allow optimal light penetration and signal detection. The vaginal probe was inserted into the vagina using regular specula and placed on the vaginal portion of the uterine cervix with a gentle pressure ensuring good probe-cervix contact but without alteration of perfusion. Perfect placement of the probe can be easily performed and controlled. Measurements were performed once on the anterior and once on the posterior cervical lip. For technical reasons the anterior cervical lip was more suitable to FD-NIRS measurements. This is why we restricted data analysis to those of the anterior cervical lip.

Optical properties were obtained from 10 patients. Oxy- and deoxyhemoglobin (μM), total hemoglobin (μM), oxygen-saturation and water (in percent) were calculated based on the absorption (μ_a) of light. Results were presented as mean values, mean relative changes $\pm$ standard error of the mean. The paired Student's t-test was used to calculate statistical significance: $P < 0.05$ was considered to be significant and $P < 0.005$ as highly significant.

Scattering values (μ'_s) were presented for the different wavelengths (690, 730, 750, 808, 870, 920, and 970 nm). The mean scattering across wavelengths and its change were calculated. In addition, the wavelength-dependent decrease of scattering (scatter power) was calculated by an exponential fit. The significance of changes was tested with the Wilcoxon test.

RESULTS

Figure 2 shows absolute concentrations of HHb, O_2Hb, tHb in the tissue of the uterine cervix prior to (white bars) and after (gray bars) drug-induced cervical ripening. StO_2 and H_2O are calculated as percentual tissue fractions.

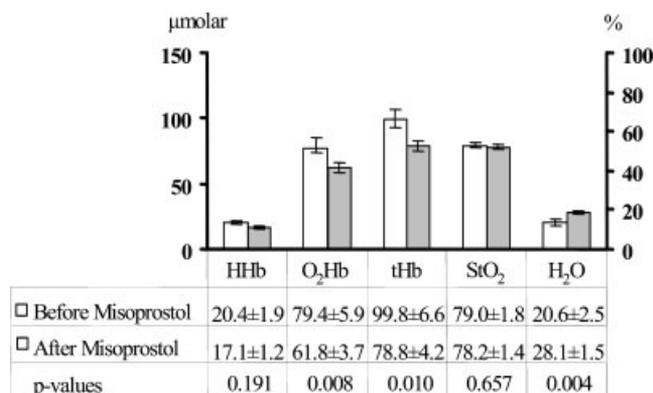|	HHb	O_2Hb	tHb	StO_2	H_2O
☐ Before Misoprostol	20.4±1.9	79.4±5.9	99.8±6.6	79.0±1.8	20.6±2.5
☐ After Misoprostol	17.1±1.2	61.8±3.7	78.8±4.2	78.2±1.4	28.1±1.5
p-values	0.191	0.008	0.010	0.657	0.004

Fig. 2. Diagram showing the mean values in micromolar for deoxyhemoglobin (HHb), oxyhemoglobin (O_2Hb), and total hemoglobin (tHb) and the mean values in percent for oxygen-saturation (StO_2) and water (H_2O) before (white bars) and after (gray bars) drug-induced cervical ripening. The line within each bar represents the $\pm$ standard error of the mean.

Misoprostol induced a decrease in total hemoglobin of $21 \pm 6\%$ ($P < 0.05$), a decrease in oxyhemoglobin of $22 \pm 6\%$ ($P < 0.05$), a decrease in deoxyhemoglobin of $16 \pm 11\%$ (not significant) and an increase of $36 \pm 8\%$ ($P < 0.005$) in water content. A not significant downward drift in the oxygen-saturation was detected.

The mean light scattering across all wavelengths did not change prior to and after drug-induced cervical ripening ($\Delta\mu'_s = -0.081$/cm; Confidence Interval 95% -0.476 to 0.313). However, the scatter power was significantly lower ($P < 0.05$) after drug-induced cervical ripening (Fig. 3).

DISCUSSION

Detection and prevention of preterm labor is one of the most challenging problems in modern obstetrics. This study employed modern technology to measure optical properties of the human uterine cervix. Measurements were performed in patients with drug-induced cervical ripening for technical abortion as a reproducible and easily accessible model for cervical ripening. We provide new insight into the physiological changes during pregnancy leading to cervical ripening.

The human uterine cervix is a complex tissue composed of an extracellular matrix consisting predominantly of collagen with elastin and proteoglycans, and a cellular component consisting of smooth muscle and fibroblasts, epithelium, and blood vessels [9]. Hormone-regulated biochemical changes occur during pregnancy, ultimately leading to cervical ripening [10]. Prostaglandins (PG) are widely used in pregnant women for cervical ripening and induction of labor. PG initiates a remodeling of the cervical connective tissue resembling the spontaneous ripening process [11–13].

Various biochemical pathways lead to changes of the uterine cervix during pregnancy [10]. A decrease in collagen concentration and an increase in water content are known to substantially contribute to these changes. Inflammation cells invade the tissue and release cytokines [14]. These cytokines stimulate the production of metalloproteinases that cause collagen degradation and decreased collagen content. The activity of the fibroblasts changes, resulting in an increased production of glycosaminoglycans, mainly hyaluronic acid, and a reduced secretion of collagen. Hyaluronic acid has a high affinity for water and attracts water molecules. Nitric oxide (NO) may be involved in the process of cervical ripening and may cause the inflammatory-like changes inducing arterial dilation, leakage of fluid to the extracellular matrix, and leukocyte infiltration [15]. Nitric oxide may also regulate the activity of the metalloproteinases and induce prostaglandin production by stimulating cyclooxygenase activity [16].

The clinically evident softening of the cervical tissue may in part be explained as decrease in collagen concentration combined with an increase in water content. We believe that this clinical finding is represented in our measurements. As shown in Figure 2, misoprostol-induced cervical ripening resulted in a dramatic increase in water content by
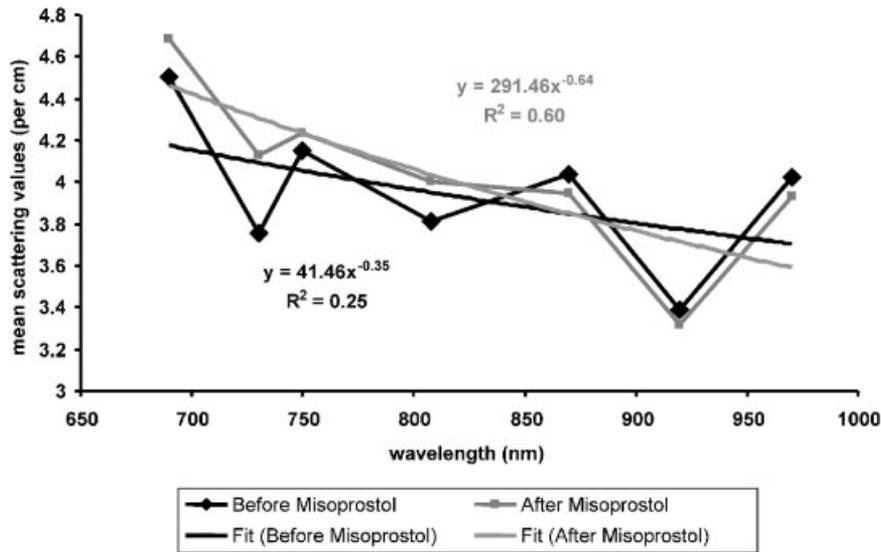
Fig. 3. Wavelength-dependent decrease of scattering (scatter power) and its exponential fit before (black) and after (gray) drug-induced cervical ripening. $R^2 =$ coefficient of correlation.

36%. This in turn, fits well into the above described biochemical cascade. On the other hand, our study revealed a relative reduction of tHb. Although this appears to be contradictory, this decrease in tHb is likely to be a consequence of the increased water content in the tissue, representing tissue edema. While the absolute perfusion in each vessel can be assumed to rise, the increased water content of the extracellular matrix results in an increase of the distance between vessels. Thus, the perfusion per tissue fraction is relatively lowered although the perfusion per diameter and time of the vessels is increased. O_2Hb decreased 22% while HHb decreased only 16%. This may reflect an oxygen consuming process in the cervix during cervical ripening. Whether the oxygen is metabolized by inflammation cells or is used for biochemical processes during degradation of the extracellular matrix is not known.

The number of apoptotic cells increases and that of proliferating cells decrease as pregnancy advances [17,18]. Apoptosis is a phenomenon characterized by cell shrinkage and cleavage of chromatin [10]. Scattering of light is a boundary phenomenon. As photons propagate in tissues and hit on boundaries, such as cellular membranes, there is a change in refractive index resulting in a change of the photon's direction, the so-called scattering of light. The scatter power depends on the size distribution of the intra- and extracellular scatterers which change during apoptosis and extracellular matrix remodeling. In our measurements, we observed a significant decrease in the scatter power explainable by the shrinkage of the cellular components of the uterine cervix after programmed cell death. On the other hand, oxygen saturation decreased only slightly during treatment with misoprostol (Fig. 2). Although it can be assumed that the drug-induced inflammatory process resulted in an increased oxygen

consumption of the tissue this seems to be counterbalanced in part by the reduced oxygen requirement of the tissues undergoing apoptosis.

The decrease in the scatter power could also be explained by the changes in the collagen ultrastructures. Under cervical ripening the concentration of collagen decreases from insoluble to more soluble collagen by an increase of collagenolytic activity. The collagen is dispersed and remodeled with a net loss in collagen fiber alignment and a decrease in fiber length [10]. This shift in the length and size of the collagen could again be seen in our measurements in the decrease in scatter power. This is an excellent agreement with the clinical findings of the smoothened and thus ripened cervix.

One of the major purposes in the clinic, however, is the identification of women at risk of preterm delivery. The current state of labor monitoring is highly subjective and no currently used method has been so far successful at predicting preterm delivery.

Digital vaginal examination (i.e., bimanual vaginal assessment of the uterine cervix), transvaginal ultrasonography, and fetal fibronectin (FFN) have emerged as the major clinical predictors of preterm birth [19]. New techniques are being developed for assessing more objectively the cervical changes, but clinical studies are still needed to define the value of these new methods in clinical practice.

The most remarkable advances have been made in measuring the length of the uterine cervix by transvaginal ultrasound [20]. However, some studies reveal that the measurement of cervical length by ultrasonography does not provide more relevant information than digital examination in a population presenting with preterm labor [21]. Furthermore, the tissue specific mean gray scale value distribution of the cervix determined by quantitative

ultrasound gray level analysis has been observed to be a better predictor for preterm birth than cervical length measurement [22]. Our data may, in part, add to the clarification of the gray level analysis as performed by ultrasound. Since water appears typically black in sonography, the gray scale may be due to variations in water content as evidenced by our data. The combination of transvaginal sonography with its capability to measure the cervical length, the cervical gray scale and the vessel perfusion may indeed reveal additional information when combined with FD-NIRS.

Cabrol et al. [23] designed a cervicotonometer used to measure cervical distensibility, reflecting cervical maturation: cervical distensibility was significantly elevated in women who had a preterm delivery. Mazza et al. [24] used an "aspiration device" [25] to characterize the in vivo mechanical properties and the stiffness of human uterine cervix. The preliminary data indicate that the stiffness parameter may detect early changes associated with pathologic conditions. But the design of the instrument would probably limit its wider use in clinical practice. On the other hand, the use of an FD-NIRS instrument as proposed in the present study seems to provide similar information without any known side effects or risk for the pregnancy.

Magnetic resonance imaging (MRI) [26] studies of the uterine cervix measured an increase in signal intensity with increased gestational age. This is probably related to the decrease in collagen content and the increase in hydration. The results are still too approximate and the technique too complicated to allow an exact prediction of preterm delivery in clinical routine. However, data from MRI studies support our findings. Our results show physiologic changes during cervical ripening that fit well to the rather anatomic examinations of the MRI. Thus, MRI and FD-NIRS may be complementary to one another.

The uterine electromyography (EMG) acquires uterine electrical signals taken non-invasively from the abdominal surface [27,28] and may predict labor and subsequent delivery. But clinical studies are still needed to allow the predictive value of these new methods in clinical practice.

A biochemical approach for the assessment of the cervix would require cervical biopsies and cannot be used in practice. An indirect approach is the measurement of biomarkers involved in cervical ripening. Among many markers evaluated, FFN is an effective short-term marker of preterm delivery [29,30]. No individual serum biomarker is useful when used alone in a symptomatic low-risk obstetric population, but the concept of a "multiple marker" approach may improve the predictive ability [31]. We believe that our FD-NIRS system is capable to provide important information on physiologic changes and that our system fits well into a "multiple marker" concept.

The histological changes in the cervical tissue of the ripened cervix can be assessed by samples of cervical tissue, but again this is not possible in practice. A non-invasive method for the measurement of the decrease in collagen content has been developed by Garfield and co-workers [32,33]: light-induced fluorescence (LIF) of the cervical collagen at a typical wavelength of 390 nm can be measured using a "Collascope." The correlation between gestational age and cervical tissue collagen content is high. However, the clinical evaluation is still in progress. Our FD-NIRS instrument can easily be modified to introduce LIF measurements. A combination of scattering and fluorescence parameters may indeed deepen our insight into cervical physiology in pregnancy.

FD-NIRS is capable of quantifying absolute tissue μ_a and μ'_s values and absolute concentrations of tissue O_2Hb, HHb, tHb, StO_2, and H_2O. Our encouraging results indicate that FD-NIRS is a promising diagnostic tool to detect changes in the tissue content of hemoglobin and water, representing cervical perfusion. In combination with the scattering of light FD-NIRS provides useful information regarding the status of the cervix in relation to the ripening. The potential benefits of FD-NIRS include a better understanding in physiology and biochemistry of cervical ripening and eventually a prediction of preterm labor. We therefore propose this technology to assess the cervical status for example before the induction of labor or for the differentiation between true and false labor. In our ongoing studies, we investigate changes of the uterine cervix in various stages of normal pregnancy and compare them with those of pregnancies at risk for preterm delivery in order to predict preterm labor.

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Curriculum Vitae

Persönliche Angaben

Name und Vorname	Baños Ana
Geburtsdatum	27.07.1974
Geburtsort	Männedorf
Bürgerort	Uetikon am See ZH

Schulen

1981-1987	Primarschule in Uetikon
1987-1990	Realschule in Uetikon
1990-1991	Weiterbildungsklasse in Küsnacht
1991-1995	Gymnasium Juventus in Zürich
	Matur Typus D

Studium

1995-2003	Studium der Humanmedizin an der Universität Zürich
11/2003	Eidgenössisches Staatsexamen, Medizinische Fakultät, Universität Zürich

Praktische Tätigkeiten

02/2004-07/2005	Assistenzärztin Gynäkologie und Geburtshilfe Kreisspital Männedorf
10/2005-06/2007	Wissenschaftliche Mitarbeiterin Forschungsabteilung Gynäkologie und Geburtshilfe Universitätsspital Zürich
seit 07/2007	Assistenzärztin Gynäkologie und Geburtshilfe Universitätsspital Zürich