THE BEHAVIOR OF THE UTERINE CERVIX DURING LABOR

Cover: Dilatation. Karin van Bragt. 1992

THE BEHAVIOR OF THE UTERINE CERVIX DURING LABOR

(HET GEDRAG VAN DE CERVIX UTERI TIJDENS DE BARING)

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. C.J. RIJNVOS
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 23 DECEMBER 1992 OM 15.45 UUR

DOOR

HENDRICUS JACOBUS HUBERT MARIE VAN DESSEL

GEBOREN TE BERGEN OP ZOOM

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Promotiecommissie

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vraghe. Hoe kan men de ontsluytinghe van de Binne-mond, vande Baer-moeder weten?

Antw: Door het ghevoelen.

vraghe. Op wat maniere kan men dat ghevoelen?

Antw: Dat kan men wel ghevoelen, als men de twee voorste vingheren, die met Olie bestreken moeten zijn, in het lichaem van de baerende Vrouwe bryngt.

From: "Ampt ende Plicht der Vroed-Vrouwen" by Cornelis Kelderman. 1697

Aan Yolande
Marle, Flore, Rymme

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Chapter 1

INTRODUCTION

Little appears to be known about the relationship between behavior of the uterine cervix and myometrial activity during the first stage of labor.[135] Considering the extensive medical and social problems related to dysfunctional behavior of the cervix during parturition, the lack of knowledge of cervical physiology and pathophysiology during labor is surprising. Labor dystocia, i.e. the failure of the cervix to dilate despite adequate uterine contractions, is the single factor that has contributed most to the increase in cesarean deliveries.[7] On the other hand, preterm delivery is the most significant contributor to perinatal morbidity and mortality in the Western world.[74] A better understanding of the physiology of cervical dilatation in relation to uterine contractions might contribute to the solution of these obstetric dilemmas.

In order to improve the knowledge of the physiologic changes of the cervix during parturition, a reliable technique for monitoring cervical behavior during labor is indispensable. Until recently digital examination of the cervical os by the attending obstetrician was the only method available to assess the condition of the cervix during parturition. Using digital palpation of the cervix, Friedman demonstrated that the curve of cervical dilatation plotted against time is sigmoid-shaped.[32] Although useful in everyday clinical practice, digital examination has major shortcomings. The inter-observer variability is considerable[119] and the intermittent nature of the procedure does not allow an assessment of the dynamics of the cervix during labor.[38] Despite these disadvantages, the knowledge of cervical changes during labor depends almost exclusively on data obtained by digital examination.

For research purposes *ultrasound cervimetry* seems to be the method of choice for measurement of cervical dilatation during labor.[59] The ultrasound cervimeter uses two miniaturized transducers that are attached to the cervix to measure cervical dilatation during the first stage of labor. The method offers continuous recording of cervical dilatation during labor and can easily be combined with measurement of intrauterine pressure, thus allowing the assessment of cervical dynamics during labor. Interesting and promising results have been published in a preliminary report.[59] For the first time, cervical dilatation patterns were objectively established. However, insufficient clinical data are available to assess the potentials of ultrasound cervimetry and a thorough evaluation of its value is imperative.

A second handicap for the study of cervical behavior during labor is the lack of insight into the mechanisms of control of cervical dilatation.[18] Several observations suggest that prostaglandins are involved in the achievement of successful effacement and dilatation of the cervix, once cervical ripening is established. Prostaglandins have been shown to be important regulators of the physiology of the cervix during pregnancy, in particular during the last trimester.[10] Concentrations of prostaglandin E_2 en $F_{2\alpha}$ rise markedly at the onset of labor[55,56] and the accumulation of prostaglandins is less in labor progressing slowly than in labor of normal duration.[96] However, thorough studies of prostaglandin-mediated cervical changes during labor are lacking.

This thesis presents the results of several experimental and literature studies to evaluate cervical behavior during labor. The following questions were specifically addressed:

- can ultrasound cervimetry be used for the study of cervical behavior during labor?

- do prostaglandins play a role in the control of the cervix during the first stage of physiologic labor?

Ultrasound cervimetry was compared to various other methods used for measurement of cervical dilatation during labor and evaluated in an experimental study of 67 women in labor. The role of prostaglandins in the cervix was assessed on the basis of the available literature and investigated in an experimental study in 32 primiparous women in physiologic labor. The interpretation of cervical dilatation and intrauterine pressure signals required the development of a program for computer-aided analysis which is also presented in this thesis.

Chapter 2

ASSESSMENT OF CERVICAL DILATATION DURING LABOR*

2.1 Introduction

The problems associated with measurement and recording of cervical dilatation during labor constitute major obstacles for the study of cervical behavior during labor. In addition to the simple method of digital examination of the cervical os, a variety of more or less complicated instruments have been developed to assess cervical dilatation for clinical and scientific purposes. This chapter presents and discusses the various methods for assessment of cervical dilatation as reported in the literature, in an attempt to evaluate their validity and usefulness.

2.2 Digital cervimetry

Our current knowledge of cervical behavior depends largely on data obtained by repeated digital palpation or 'digital cervimetry' during labor. Both vaginal and rectal examination have been used. The latter method was advocated by Kroenig[63] to prevent ascending uterine infection. Semmelweiss' classic work involving the relationship between vaginal examination and puerperal infection is well appreciated.[104] However, there is no evidence that palpation of the cervix with a finger introduced into the rectum prevents ascending infection: during rectal examination the vaginal wall and contents are brought into close contact with the cervical canal. When appropriate aseptic measures are taken, vaginal examination does not endanger the patient and reveals more details than palpation by way of the rectum.[73] Women's preference for vaginal over rectal examinations was clearly demonstrated.[77] Some authors, however, continue to

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* The main substance of this chapter was published in : Van Dessel T, Frijns JH, Kok FT, Wallenburg HC. Assessment of cervical dilatation during labor: a review. Eur J Obstet Gynecol Reprod Biol 1991;41:165-71.

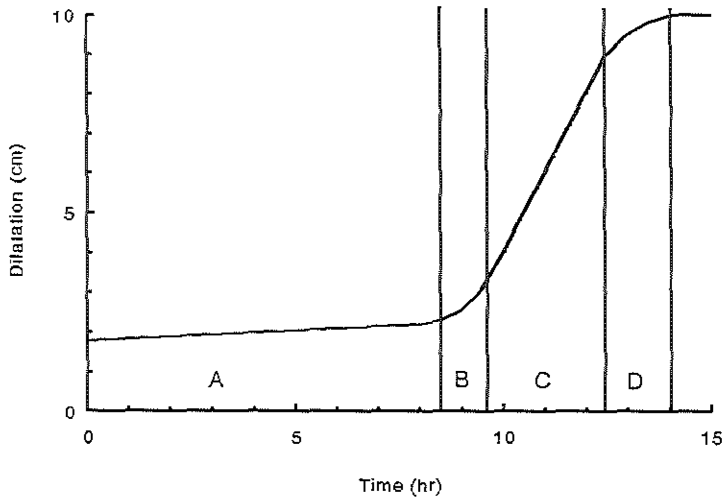

Figure 2.1. Cervical dilatation curve after Friedman. (A: latent phase. B: acceleration phase. C: phase of maximum slope. D: deceleration phase).

recommend rectal examination.[82]

Results of measurement of cervical dilatation by digital examination are markedly influenced by experience of the examiner and inter-observer variability is considerable.[38] An experiment with a set of cervical dilatation simulators demonstrated marked inaccuracy in the assessment of cervical dilatation, even in a group of experienced obstetricians and midwives.[119]

Many reports in the literature stress the importance of graphic recording of progress in cervical dilatation for clinical management of labor.[19,20,67,91,114] Using data obtained by digital, mainly rectal, examination Friedman constructed the now classic cervical dilatation curve,[32,33,34,35,36] as shown in figure 2.1.

Although digital examination offers valuable clinical information on the progress of labor, its intermittent character does not allow an assessment of the dynamics of cervical dilatation. For that reason many attempts have been made to construct devices, cervimeters, for objective and continuous measurement of cervical dilatation based on (electro)mechanical, electronic and ultrasonic principles. An historical overview of the various instruments published since the early fifties is presented in Table 2.1.

Table 2.1. Historical overview of cervimetric techniques.

Author	Year	Principle	Reported accuracy	Method of measurement	Method of recording	Number of patients
Wolf	1951	electromagnetic	-	induction coils	electrical	0
Smyth	1954	electromechanical	-	cervix strings	electrical	0
Siener	1956	mechanical	-	intravaginal calipers	pneumatic	35
Friedman	1956	mechanical	0.5 mm	intravaginal calipers	none	25
Siener	1957	mechanical	'not'	cervix strings	pneumatic	55
Langreder	1959	electromechanical	-	intravaginal calipers	photoelectric	0
Siener	1961	electromechanical	-	intravaginal calipers	electrical	20
Vossius	1961	electromechanical	0.25 mm	intravaginal calipers	electrical	0
Kazda et al.	1962	electromechanical	-	intravaginal calipers	electrical	90
Friedman	1963	electromechanical	1 mm	intravaginal calipers	electrical	0
Tervilä	1963	mechanical	-	intravaginal calipers	none	0
Wurm	1967	electromechanical	-	intravaginal calipers	electrical	1
Krementsov	1968	mechanical	-	intravaginal calipers	none	0
Rice	1974	electromagnetic	-	induction coils	electrical	0
Kriewall	1974	electromagnetic	-	Hall-effect transducer	electrical	0
Richardson	1976	mechanical	1 cm	intravaginal calipers	electrical	21
Zador et al.	1976	ultrasonic	1-2 cm	ultrasound transducers	electrical	24
Kok et al.	1976	ultrasonic	0.3 cm	ultrasound transducers	electrical	62
Moss et al.	1978	ultrasonic	0.6 cm	ultrasound transducers	electrical	13

2.3 (Electro)mechanical cervimeters

Two main prototypes of mechanical cervimeters have been described, the calipers- and the string-type.

In the basic calipers-type cervimeter, calipers equipped with a centimeter rule at the distal end are used to measure the distance between opposing cervical rims (Fig. 2.2). The Krementsov cervimeter,[61] called an 'orificiometer' , has a ring at each proximal caliper end in which the fingers of the examiner can be placed. It enables the examiner to verify his findings by vaginal examination. The Tervilä cervimeter[117] consists of two pairs of Kelly clamps, attached separately to the cervical edges, and connected in a hinge-like way. The Friedman cervimeter[36] is equipped with bulldog clips for attachment to the cervical rims. Measurement is continuous, but readings are obtained at 2 to 10 minute intervals and plotted manually against time. In contrast to the Krementsov and Tervilä cervimeters, which were apparently never applied in clinical studies, the Friedman device was used in 25 women in labor. The cervical dilatation curves obtained in these patients show a sigmoid shape. Disadvantages of these simple mechanical cervimeters are the discontinuity of readings, the lack of recording facilities and the quite heavy mechanical construction that interferes with dilatation during measurement.

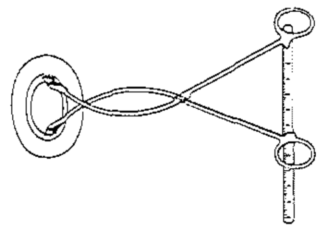

Figure 2.2. Mechanical cervimeter according to Friedman

In later years low-weight calipers with cervical attachment clips were combined with potentiometers to convert the movements of the caliper arms into an electrical signal that could be recorded on a polygraph (Fig. 2.3). Electromechanical cervimeters of this basic type were described by Vossius,[134] Svoboda[116] and Richardson et al.[98,99] The electromechanical Friedman cervimeter,[37] is attached to the cervix by a retractable row of needles. At a preset dilatation the needle attachments to the cervix are automatically released. In the instrument developed by Langreder[66] movements are recorded by means of a photoelectric cell. The cervimeters described by Warm[136] and Kazda and Brotanek[53] have a similar design. A pair of calipers is connected to an invisible

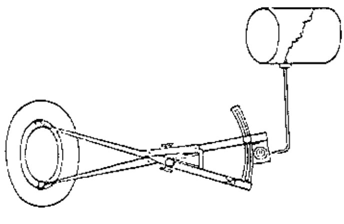

Figure 2.3. Electromechanical cervimeter according to Siener.

hinge in a heavy extravaginal part containing an internal potentiometer. Kazda and Brotanek report successful recordings in 90 patients without presenting data. Siener has reported several cervimeters. The original Siener cervimeter,[108,109,110] also reported by Embrey and Siener,[30] offers the opportunity for both measurement of cervical dilatation and measurement of cervical dilatation forces, after fixation of the calipers. Siener has used the concept of the electromechanical calipers cervimeter to construct even more sophisticated devices: the cervical dynamometer[107] and the 'erweiterte Zervixwehen-messer' ('expanded cervix-contraction meter').[105] The cervical dynamometer allowed measurement of the pressure of the fetal head on the cervix after fixation of the intravaginal arms of the cervimeter. The 'expanded cervix-contraction meter' combined a calipers cervimeter with a metal construction for measurement of fetal descent. Some mechanical calipers cervimeters use a pneumatic instead of an electrical signal transmission system.[105]

The string-type cervimeter consists of strings or cords, attached to the cervix (Fig. 2.4). Changes in dilatation cause changes in length of the strings which are transmitted to a kymograph by a mechanical pulley-guided system[106] or electrically by a linear differential transformer.[111]

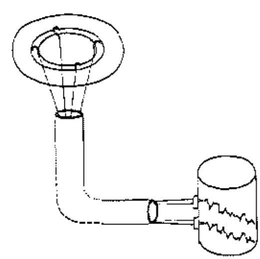

Figure 2.4. String-type cervimeter according to Siener.

Some instruments are

described for assessment of cervical properties other than dilatation. Glass and coworkers used the medical engineering principle of indentation to design an electromechanical device for measurement of the relative softness of the cervix.[39] An instrument to measure the amount of pressure of the fetal head on the cervix has been reported by Noack and Blaschkowski.[79]

2.4 Electromagnetic cervimeters

Electromagnetic cervimeters were described by Wolf[137] in a congress report and later by Rice[97] in a doctoral thesis. With these cervimeters cervical dilatation is measured using two small induction coils, attached to opposing cervical rims (Fig. 2.5). An electrical current, sent through one of the coils, establishes a magnetic field that is detected in the opposite coil and then recorded. Kriewall has used a permanent magnet dipole as a magnetic field source and two Hall-effect magnetic-field transducers as detectors.[62] The signals derived with this technique are processed to determine the distance between the transducers. These publications concerning electromagnetic cervimeters are not easily accessible, and data on the clinical application of this type of cervimeter could not be found.

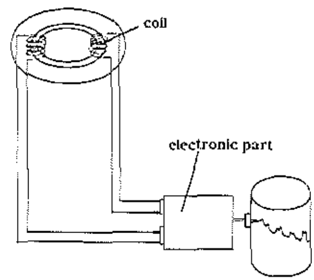

Figure 2.5. Electromagnetic cervimeter according to Wolf.

2.5 Ultrasound cervimetry

Abdominal,[89,102,129] vaginal,[3,64] and transperineal[48,70] routes have been used to visualize cervical dilatation by means of ultrasound during pregnancy. Most attempts are directed towards the diagnosis of premature labor[1] or cervical incompetence.[50] However, no reports could be found in the literature dealing with systematic visual assessment of cervical dilatation during labor.

A different approach uses an ultrasound cervimeter consisting of two transducers attached to opposing rims of the cervix (Fig. 2.6). An ultrasonic signal generated by one transducer is received by the opposing one. Since the ultrasound velocity is known, the transmission time allows computation of the distance between the transducers. The first ultrasound cervimeter was described by Zador et al. in 1974,[139,140] who used spring-loaded clips to attach the transducers to the cervix. A total of 24 readings of women in labor were reported, but no specific data were given. Apparently, practical problems were encountered, because further clinical studies with this device could not be found. A similar cervimeter has been presented by Kok et al. in 1976 in preliminary reports.[27,59] The problems with the fixation of the transducers to the cervix were eliminated by using special spiral-shaped transducers that were screwed into the cervical rim. The obtained data were analyzed off-line by a computer, and accuracy and precision in vitro and in vivo were shown to be good in a well-documented study of 62 women in labor.[60] Cervical dilatation appeared to follow a wave pattern reflecting the intrauterine pressure curve. Maximal cervical dilatation coincided with the maximal intensity of each contraction. Generally, the derived curve of cervical dilatation during labor showed the sigmoid shape postulated by Friedman.[38] A decelerative phase was never detected. Using a similar device Moss et al. investigated 13 women in labor.[75] Contrary to the findings reported by Kok et al.,[60] this author observed that the peaks of uterine contraction and cervical dilatation were out of phase.

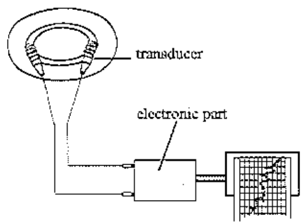

Figure 2.6. Ultrasonic cervimeter according to Kok.

2.6 Conclusion

The available reports indicate that mechanical cervimeters are cumbersome in clinical practice and cannot be used for continuous measurement of dilatation. Most electromechanical devices offer the possibility of continuous registration but they have the disadvantage of a heavy mechanical intravaginal part, which may interfere with cervical dilatation. Electromagnetic cervimeters with clinical applicability have not been described. Ultrasound visualization of the cervix may be helpful in monitoring the patient at risk for preterm delivery, but it does not allow continuous registration of dilatation during labor. The ultrasound cervimeter allows continuous and reliable recording of cervical behavior with little discomfort to the patient, but clinical experience and data are still limited. Ultrasound cervimetry may be a useful research tool for the study of the cervical response to the uterine contractions during labor.

Chapter 3

ULTRASOUND ASSESSMENT OF CERVICAL DYNAMICS DURING THE FIRST STAGE OF LABOR

3.1 Introduction

Little is known about cervical dilatation patterns during labor. As discussed in chapter 2, the scarce available knowledge is obtained by digital examination of the cervix, which is an unsuitable method of assessment for the study of cervical behavior during labor. Using rectal and vaginal examinations Friedman demonstrated that the cervical dilatation curve is sigmoid-shaped and has a latent phase and an acceleration phase (as shown in the previous chapter in fig. 2.1). The first is characterized by an absent or slow rise in cervical dilatation during several hours, whereas during the latter a sudden increase of cervical dilatation speed occurs.[38]

As outlined in chapter 2, the ultrasound cervimeter appears to be a valuable tool for the investigation of cervical behavior during labor. In combination with a tocograph, the ultrasound cervimeter provides continuous quantative data on cervical dynamics during labor. On the whole, the cervical dilatation curves obtained by ultrasound cervimetry (fig. 3.1) were found to be comparable to the curves described by Friedman.[59] Ultrasound cervimetry results showed, that in the early latent phase the cervix did not show dilatation reactions in response to uterine contractions. Then, starting later in the latent phase at the so-called *reaction point*, a temporary gain in cervical dilatation is noticed during the contractions. Finally, after the *acceleration point*, where the acceleration phase begins, cervical dilatation speeds up until full dilatation is reached.

This chapter evaluates the value of ultrasound cervimetry for the study of the cervical dynamics during spontaneous and oxytocin-induced labor. In order to describe cervical dilatation and intrauterine pressure patterns, the following variables describing the dynamics of labor will be assessed: the reaction and acceleration point, contraction work to reach full dilatation and the mean increase in cervical dilatation during contractions.

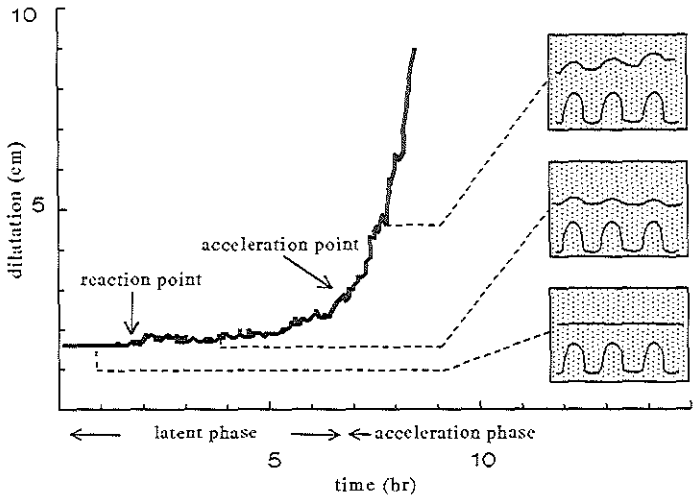

Figure 3.1. Ultrasound cervimetry partogram. The insets show the typical dilatation (top) and pressure (bottom) tracings at the indicated time.

3.2 Material and Methods

Patients

Subjects were recruited from pregnant women under obstetric care in the antenatal clinic. The women selected met all of the following criteria: 1. uncomplicated pregnancy with a single fetus in cephalic position; 2. duration of pregnancy between 38 and 42 weeks; 3. admission to the labor room in the first stage of spontaneous labor or for elective induction of labor. Spontaneous labor was defined as the occurrence of regular painful contractions every 3 to 5 minutes in a woman with a cervix score according to Burnhill of 6 or more.[9]

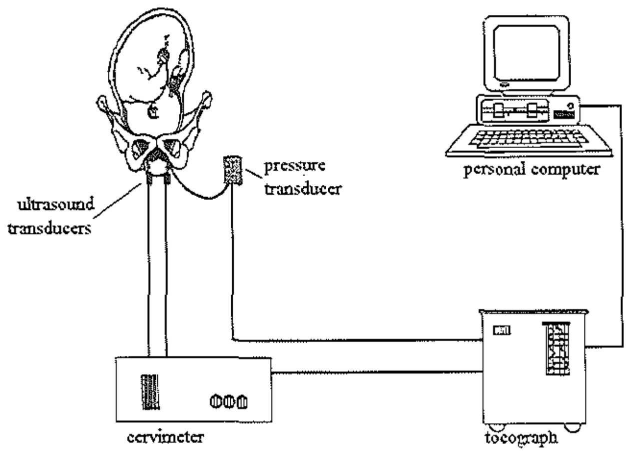

Figure 3.2. Diagram showing the combined use of ultrasound cervimetry and intrauterine tocography.

Elective induction of labor was defined as induction of labor in the absence of a medical-obstetric indication for termination of pregnancy[130] and was performed in the presence of a cervix score of 6 or more only.

Sixty-seven term parturients gave their informed oral consent and were enrolled in the study. Of the 67 recordings, 5 were of insufficient quality, mainly due to early disconnection of the cervical transducers; 62 recordings were used for further analysis. They were divided into four groups: nulliparous women in spontaneous (n=9) or oxytocin-induced labor (n=26), and parous women in spontaneous (n=11) or oxytocin-induced labor (n=16).

Instrumentation

For the study described in this chapter the cervimeter developed in the Erasmus University School of Medicine and Health Sciences[27] was combined with intrauterine tocography[59] (fig. 3.2). The basic principle is simple. Two ultrasound transducers (fig. 3.3), composed of barium titanate, set in stainless steel cylinders with a length of 5 mm, a diameter of 4.5 mm, and a weight of

0.3 g, are attached to the lateral rims of the external cervical os with a specially designed guide tube. Pulsed 0.6 MHz ultrasound signals are generated with a 200 Hz repetition frequency in one transducer and received by the other. As the ultrasound velocity is known (approximately 1500 m/s in all tissues involved,[60] the travelling time of a pulse between the transducers can be used to calculate the distance between the transducers that represents cervical dilatation.

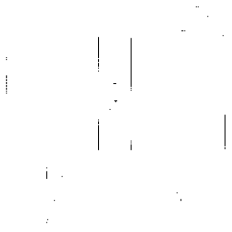

Figure 3.3. The ultrasound transducers.

In practice, the membranes were ruptured and an electrode was attached to the fetal scalp for fetal heart rate monitoring. A water-filled, open-tip pressure catheter was introduced into the uterine cavity through the cervix. The electrode and the intrauterine catheter were connected to a Hewlett Packard 80300 fetal monitor. The two coiled cervimeter transducers were screwed into the lateral rims of the cervix at 3 and 9 o'c lock, respectively, with a special guide tube and connected to the cervimeter. Cervical dilatation, intra-uterine pressure and fetal heart rate were

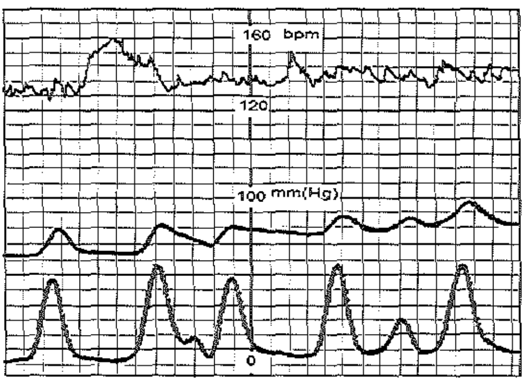

Figure 3.4. Original tracing obtained from a parous woman showing the fetal heart rate (top), cervical dilatation (middle) and intrauterine pressure (bottom) signals.

recorded simultaneously on a polygraph with a paperspeed of 3 cm/min (fig. 3.4). The electrical outputs of the cervimeter and the tocograph were sampled with a frequency of 1 Hz and stored for off-line computer analysis.

Signal analysis

In order to eliminate the high-frequency noise component in the low-frequency signal, low-pass filtering was performed before analysis. Both intrauterine pressure and cervical dilatation signals are characterized by a constant or slowly rising resting level interrupted by episodic wave-like elevations. Because of the similarity in shape of pressure and dilatation signals, an identical principle of analysis, based on the first and third time derivative, could be applied. An empirically determined threshold of the first time derivative of the filtered signal of the intrauterine pressure curve of 0.2 mmHg/sec and of the cervical dilatation curve of 0.007 cm/sec was considered to mark the beginning and end of the signal changes (fig. 3.5). The maximum of a contraction or cervical dilatation reaction is represented by the value 0 in the first time derivative curve. The principles of filtering and analysis will be discussed in full detail in chapter 6. The gain (cm) in cervical dilatation during a myometrial contraction will be referred to as the **cervical dilatation reaction**. The **cervical reaction time** is defined as the time (sec) between the onset of a myometrial contraction and the start of the corresponding cervical reaction. The **reaction point** is defined as the cervical dilatation (cm) at which a cervical reaction occurs for the first time. The **acceleration point** marks the end of the latent phase and the beginning of the cervical acceleration phase and is defined by the dilatation (cm) at which the third derivative of the filtered dilatation signal

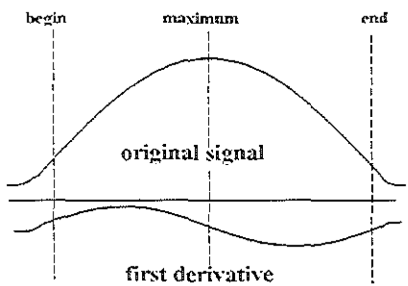

Figure 3.5. Original signal (top) and first derivative (bottom). The start and end or maximum of a signal change are determined using the first derivative.

reaches the value 0. Mean contraction work per cm of cervical dilatation is estimated by summation of all active pressure areas (mmHg.sec) over 1 cm of cervical dilatation.

Statistical analysis

Data are presented as medians (range) or arithmetic means (SD), as appropriate. Differences in relative frequencies between groups were analyzed with the Fisher test. Student's t (two tailed) and Wilcoxon's rank-sign test were used to assess differences, and linear regression analysis to evaluate relationships between measured continuous variables. A p-value of 0.05 was taken as the level of statistical significance.

Table 3.1. Characteristics and numbers of contractions and cervical dilatation reactions (median <range> or n values).

	nulliparous women		parous women	
	spontaneous labor (n = 9)	induced labor (n = 26)	spontaneous labor (n = 11)	induced labor (n = 16)
maternal age (yr)	28 <17-33>	23 <17-33>	28 <23-37>	28 <19-40>
gestational age (wks)	40 <38-42>	39.5 <38-42>	40 <38-42>	40 <38-42>
cervix score	8 <3-8>	7 <5-8>	8 <7-8>	6.5 <4-8>
birthweight (g)	3335 <2500-3750>	3185 <2590-4130>	3435 <2530-3935>	3455 <2430-4215>
contractions (n)	469	2565	280	1486
dilatation reactions (n)	377	1913	283	806

3.3 Results

Application of the ultrasound transducers was succesful in all women but early disconnection occurred in 5 subjects. No specific complaints were noted, and no complications occurred. Characteristics of the 62 parturients studied are summarized in Tab. 3.1. There were no significant differences in clinical characteristics between groups. 4800 myometrial contractions, and 3379 cervical dilatation reactions were included in the analysis. The significant differences in recorded contractions and dilatation reactions between groups are caused by the smaller number of patients and the shorter duration of the first stage of labor in women with a spontaneous onset of labor compared with women in whom labor was electively induced.

In general, the dilatation curves showed a latent phase followed by an acceleration phase characterized by a fast augmentation of cervical dilation. Quantative data on cervical dilatation patterns are summarized in Table 3.2. A dilatation reaction was present in all women with spontaneous labor at the start

Table 3.2. Variables of cervical dilatation in the four study groups (mean values ± SD).

	nulliparous women		parous women	
	spontaneous labor (n = 9)	induced labor (n = 26)	spontaneous labor (n = 11)	induced labor (n = 16)
dilatation at start of recording (cm)	3.4 ± 1.5	3.3 ± 0.5	4.0 ± 1.0	2.7 ± 0.8
duration of recording (cm)	2.8 ± 2.1	5.1 ± 2.0	1.2 ± 0.7	4.2 ± 2.4
reaction point (cm)	-	3.6 ± 1.0 [1]	-	2.9 ± 0.4 [2]
acceleration point (cm)	4.5 ± 1.2 [3]	4.8 ± 1.0 [4]	-	3.4 ± 0.8 [5]

1 vs. 2, $p < 0.05$
3 and 4 vs. 5, $p < 0.05$

of the recording, and for that reason the cervical reaction point could not be determined in this group. In nulliparous women in whom labor was induced, the reaction point occurred at a significantly greater cervical dilatation than in parous parturients. In the majority of nulliparous women dilatation reactions remained identical during the first stage of labor, whereas an increase in the magnitude of the dilatation reactions was observed in approximately half the number of parous women. None of the parturient women studied showed a significant alteration in cervical reaction time in the course of the first stage of labor. The efficiency of contractions, expressed as the quotient of the dilatation reaction and the active pressure area, did not change as labor progressed. In nulliparous women the acceleration point appeared to be similar in spontaneous and in oxytocin-induced labor. All parous women in spontaneous labor were apparently already past the acceleration point at the beginning of the recording.

The area of active uterine pressure remained constant during labor in all groups. The mean contraction work per cm of cervical dilatation before the acceleration point was approximately 2.5 times that after the acceleration point in all groups studied (Tab. 3.3). The mean contraction work in parous women with induced labor was approximately 60% of that in nulliparous women with induced labor, before as well as after the acceleration point. The speed of cervical dilatation before the acceleration point was similar in all groups, whereas after the acceleration point it appeared to be significantly increased in parous women with induced labor.

3.4 Discussion

In contrast to experience with various types of (electro)mechanical cervimeters as described in chapter 2, ultrasound cervimetry allows continuous, accurate and precise measurement of cervical dilatation and the application of the instrument carries little discomfort to the patient.[128] Continuous automated recording of dilatation data allows detection of the reaction and acceleration points, thus defining the first stage of labor. Other investigators have defined the

Table 3.3. Contraction work per cm of cervical dilatation and dilatation speed before and after the acceleration point (means ± SD).

	nulliparous women		parous women	
	spontaneous labor (n = 9)	induced labor (n = 26)	spontaneous labor (n = 11)	induced labor (n = 16)
contraction work per cm before the acceleration point (mmHg.sec 10^3)	55.2 ± 23.1	81.8 ± 37.2 [1]	-	50.6 ± 24.0 [2]
contraction work per cm after the acceleration point (mmHg.sec 10^3)	23.4 ± 11.1	30.5 ± 12.7 [1]	-	20.7 ± 6.4 [2]
ratio of contraction work before vs. after acceleration point	2.17	2.68	-	2.44
dilatation speed before the acceleration point (cm/hr)	0.7 ± 0.3 [3]	0.5 ± 0.5 [4]	-	0.6 ± 0.4 [5]
dilatation speed after the acceleration point (cm/hr)	2.9 ± 1.2 [6]	2.4 ± 1.0 [7]	-	3.5 ± 0.8 [8]
ratio of dilatation speed before vs. after acceleration point	4.5	6.1	-	12.5

1 vs. 2, $p < 0.05$ 3 and 4 vs. 5, no significant difference 6 and 7 vs. 8, $p < 0.05$

beginning of the acceleration phase as the cervical dilatation at which the speed of dilatation increases to a fixed value, e.g. to more than 1.2 cm/hr in nulliparous and more than 1.5 cm/hr in parous women.[90] Considering the shape of the dilatation curve, the mathematical method of using the third derivative seems to be more correct. The difference between the methods used precludes a comparison between the results presented in this chapter and those obtained by others.

The dilatation curves obtained in this study show patterns comparable to the sigmoid-shaped curves described in the original work of Friedman,[32] but we, like others[43] have never observed a deceleration phase. The deceleration phase may be an artefact due to the subtraction method used in the digital assessment of advanced cervical dilatation. Initially, the examiner estimates the distance between the palpating fingers, whereas later, when dilatation exceeds 6 cm or more, the examiner cannot feel the opposing rims anymore and subtracts the remaining rim from 10 cm.

The results of the study indicate the occurrence of important functional changes in the uterine cervix during the first stage of labor. First, in oxytocin-induced labor cervical reactions to myometrial contractions appear at 3-4 cm of cervical dilatation. These dilatation reactions can be considered indicative of increasing cervical elasticity. Second, the finding that more contraction work is needed for 1 cm of dilatation before than after the acceleration point suggests the occurrence of changes in the cervix with the acceleration point as a landmark. Third, the observation that acceleration of cervical dilatation occurs at an earlier stage and myometrial work is less in parous than in nulliparous women with induced labor indicates different cervical behavior due to the process of labor and delivery. However, parous women in induced and nulliparous women in spontaneous labor, did not differ in this respect. In contrast to the findings of Siener,[107] no significant decrease in cervical reaction time during the course of the first stage of labor was demonstrated.

The increase in cervical elasticity during labor is probably due to the histochemical changes occurring in the cervix during labor. The cervical changes appear to be independent of uterine contractions.[67,115] An extensive collagenolytic process in the cervix during parturition has been described in morphologic[51] and biochemical studies.[93] The recently proposed hypothesis that the course of the latent phase is largely determined by prostaglandin-mediated proteoglycan changes in contrast to the collagenolysis-dependent acceleration phase,[95] may offer a new perspective to understand the considerable differences in cervical behavior that exist between parturients. No histological or biochemical data are available to explain the functional differences between the cervices of parous and nulliparous women.

The results show that ultrasound cervimetry can be used for the study of the physiology and pathophysiology of cervical behavior during labor. It allows an assessment of variables of cervical dilatation in relation with intrauterine pressure during labor. In particular, the reaction and acceleration points emerge as markers of changes of the biophysical properties of the cervix. The development of appropriate soft ware for on-line analysis of these variables of cervical dilatation would be helpful for investigations into the intracervical events that explain the changes in cervical behavior around the reaction and acceleration points.

Chapter 4

PROSTAGLANDINS AND CERVICAL DILATATION

4.1 Introduction

As demonstrated in chapter 3, striking alterations in cervical behavior occur during labor. These behavioral alterations of the cervix may reflect structural changes. Prostaglandins play a key-role in the physiologic processes that determine the structure of the cervix.[10] These compounds have been shown to be important in the ripening of the cervix before the onset of active labor and the clarification of the synthesis and metabolism of these compounds has contributed considerably to our understanding of the biological control of of the cervix during labor.[72] In contrast to the vast body of literature on the relation between prostaglandins and ripening of the cervix, little is known about the role of prostaglandins during cervical dilatation. Indirect evidence suggests that prostaglandins could also be involved in the achievement of successful effacement and dilatation of the cervix, once cervical ripening is established. Concentrations of prostaglandin E_2 en $F_{2\alpha}$ rise at the onset of labor[55] and the accumulation of prostaglandins is less in dysfunctional labor than in labor of normal duration.[96]

This chapter explores the relationship between prostaglandins and cervical properties during labor on the basis of the available literature. The histological, biochemical and biophysical characteristics of the cervix before and during pregnancy and during labor will be reviewed, followed by a discussion of what is known about the mode of action of prostaglandins on the cervix. Finally, this data will be synthesized in order to develop a model that may explain the relationship between prostaglandins and the control of cervical behavior during parturition.

4.2 Morphologic and functional characteristics of the uterine cervix

The nonpregnant cervix

The human cervix measures about 2.5 cm in diameter and is predominantly composed of connective tissue, almost entirely consisting of collagen (Fig. 4.1). Some 2% of the connective tissue contains elastic fibers arrayed as a band from the periphery to the external os and upward toward the internal os.[69] The elastic fibers are located beneath layers of smooth muscle

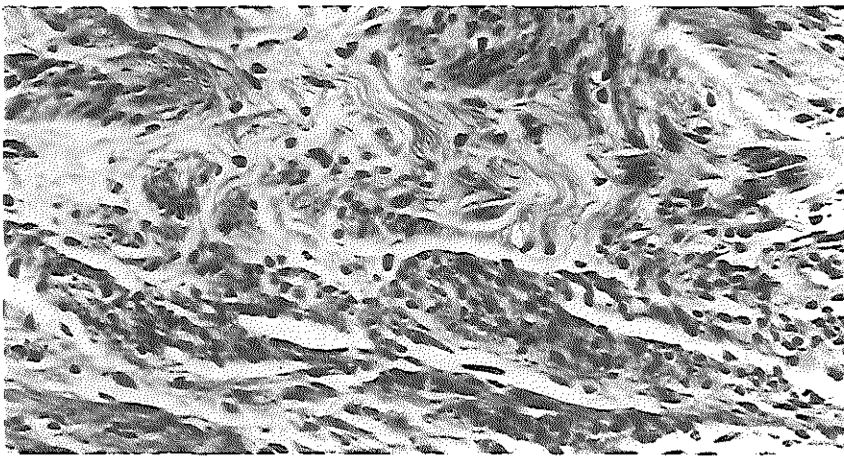

Figure 4.1. Micrograph of the cervix of a non-pregnant woman, showing dense connective tissue with many fibroblasts, and smooth muscle fibers.

cells, that account for 10-15% of the cervical substance. The main part of the smooth muscle cells of the cervix is organized in a layer that forms an extension of the myometrium along the periphery of the supravaginal portion of the cervix, with some additional scattered muscle fibers throughout the cervical body. The single layer of smooth muscle cells divides into two at the level of the vaginal reflection; one part follows the vaginal reflection, the other continues for a short distance along the periphery of the vaginal portio. The smooth muscle content decreases from approximately 25% in the upper to 6% in the lower segments of the cervix.[45] The function of elastic and smooth muscle fibers in the nonpregnant cervix is not clear, but they could be involved in maintaining cervical shape.

The fibrous connective tissue that forms the main constituent of the cervix is arranged in a superficial loose area and a dense core zone[126] and consists of a framework of collagen fibers, embedded in a ground substance or extracellular matrix. The collagen fibers determine the elasticity and the resistance to tearing, the ground substance supports the tissue plasticity, or distensibility.[135] The collagen fibers are arrayed in parallel bundles, which run in all directions and are strongly intertwined. The network is infiltrated by cells, mainly fibroblasts, that make up some 20% of the connective tissue volume.[113] The basic molecule of collagen is tropocollagen, composed of three parallel individual polypeptide chains wrapped around one another like the strands of a rope.[6] In the native collagen fibril the parallel oriented tropocollagen molecules are staggered.

The cervical ground substance is mainly composed of proteoglycans, containing a core protein to which up to a hundred macromolecular polysaccharides, or glycosaminoglycans, are attached. The dominating proteoglycan in the nonpregnant cervix is a small dermatan sulphate, named decorin, that makes up more than 75% of the ground substance, whereas hyaluronate constitutes a smaller fraction.[124] The heparan sulphate component seems to originate mainly from the vascular connective tissue.[123] The close interaction between collagen fibrils and the negatively charged proteoglycans creates stable collagen complexes, to which the connective tissue cells are connected via fibronectin.[103] The balance between internal swelling pressure, caused by hydrophilic proteoglycans, and collagen tension, provided by the collagenous ultrastructure, determines the shape of the cervix.[78] Changes in biochemical composure can thus markedly affect cervical appearance.

In vivo measurements of the force needed for dilatation[57,100] as well as in vitro stretch studies using strips of cervical tissue[22] have been performed to investigate the biophysical characteristics of the nonpregnant cervix. Both approaches show the nonpregnant cervix to be a rigid and noncompliant organ. The stretch modulus, i.e. the slope of the stress-strain curve or length-tension diagram, is high and the curve shows no yield point up to 12500 mg/mm^2 (Fig. 4.2).[22] Corresponding to the morphologic structure of the cervix, the stretch modulus is significantly lower in the periphery of the cervix compared to the region near the cervical canal.[21]

The pregnant cervix

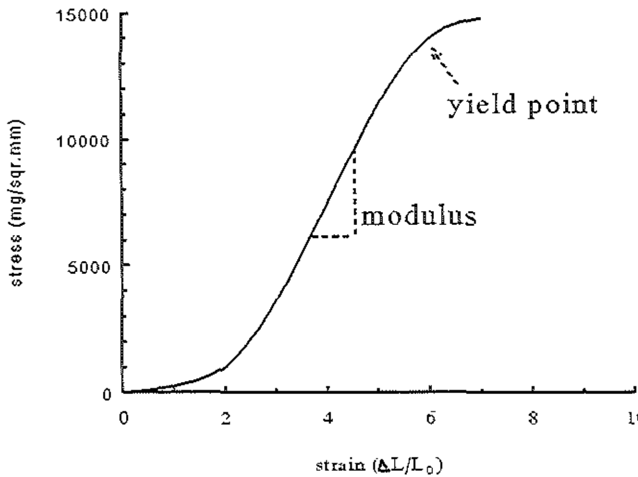

Figure 4.2 Idealized stress-strain curve obtained in vitro with elastic and collagen fibrils in parallel. L_0 = the resting length (redrawn from Conrad[23]).

During pregnancy marked structural and functional changes take place in the uterine cervix. However, the first 34 to 36 weeks of pregnancy are normally characterized by a relative inertia, which is in agreement with its static task of keeping the uterus closed. During the final weeks of pregnancy conspicuous changes occur in the shape and consistence of the cervix, generally referred to as 'cervical ripening'. These changes include increased softening and distensiblity, effacement and early dilatation.[16]

The function of elastic and muscle fibers in early pregnancy and later during cervical ripening seems to be limited. Mature cross-linked fibers may form a kind of cuff and contribute to keeping the cervix closed.[69] and a sphincter-like function has been claimed for the smooth muscle cells.[88]

Electromyographic investigations have shown a circular pattern of electrical activity in the cervix, in particular in unripe cervices of nulliparous women in early labor. This may represent circular muscle fiber activity, which might interfere with effective dilatation. Considering the constant number of smooth muscle cells in the cervix throughout pregnancy, such a sphincter-function has been questioned by others.[95,113]

It is generally agreed that connective tissue changes, including collagen degradation and alterations in the pattern of glycosaminoglycans, are at the center of cervical ripening. The swelling and softening of the cervix can be explained by a decreased resistance, due to collagen changes, to increased swelling pressure, caused by the changing proteoglycan pattern. However, the precise sequence of intracervical events is unclear and subject to much debate and controversy. Conflicting reports are the rule because of small series and differences in laboratory methods.[44,45,95,125]

Collagen breakdown is characterized biochemically by a loss of cross-links between fibers, cleavage of the triple tropocollagen helix by collagenase and elastase, and further degradation by other non-specific proteinases. The percentage of collagen breakdown during pregnancy as reported in the literature varies from 0 to 70%[25,123] and the concentration rather than the absolute amount of collagen appears to be subject to change.[12] Degradation of collagen seems to occur mainly in the third trimester of pregnancy, although a substantial reduction during the first trimester has also been reported.[123] Because Rath et al. were unable to demonstrate collagenase activity during pregnancy, they argue that enzymatic collagen degradation does not play an important role in physiologic cervical maturation.[95]

The changes in the final part of gestation in the distribution pattern of glycosaminoglycans as reported in the literature also vary widely. A substantial increase in hyaluronate and a decrease in dermatan sulphate,[132,133] as well as no change in hyalurate concentrations have been reported.[123] Rising amounts of hydrophilic hyaluronate offer a logical explanation for the increase in water content of the cervix with subsequent loosening of the connective tissue.[125] Fibroblasts are claimed to be responsible for these changes in the proteoglycan pattern before parturition.[95]

In short, it seems that the cervical connective tissue, in particular in the last part of pregnancy, is rapidly remodeling itself rather than breaking down in an absolute sense, thus developing a new architecture appropriate to new physiologic needs.[49]

Little work has been done to characterize the biophysical properties of the pregnant human cervix. The available data indicate that pregnancy reduces the stretch modulus, particularly when parturition is at hand.[22,23] Several instruments for assessing mechanical properties of the cervix in vivo have been described.[2,115,127] By means of a so-called cervicotonometer Cabrol demonstrated that, compared to nonpregnant patients, markedly reduced dilating forces were needed in term and preterm pregnant patients.[13] Using the medical engineering principle of indentation it has been shown that cervical softness increases throughout pregnancy,[39] a finding familiar to practising obstetricians using cervical palpation.

The cervix in labor

Following preparation by the marked histochemical alterations during pregnancy, the rapid dilatation during labor forms a striking finale. In the course of a few hours the closed cervix opens up and gives way to the fetus and placenta. The organization of the unlinked elastic fibers, that retract upward and inward during effacement has been claimed to be helpful for efficient dilatation.[69] Like in the lung, elastin might serve als a framework for the smooth muscle fibers to contract against. There is some electromyographic evidence of an active role of smooth muscle cells in human cervical dilatation, a common phenomenon in many species.[138] However, the combined evidence does not support an important role of elastic fibers and smooth muscle tissue. A more important function of the fiber and smooth muscle cell network could be to restore the shape of the cervix after parturition.

Several observations support the view that collagen changes determine the progress of parturition. Morphologic studies have indicated the existence of an extensive collagenolytic process[51] and several authors have reported markedly increased levels of cervical collagenase during labor.[93] The duration of cervical dilatation was found to be significantly correlated with the collagen content of the prelabor cervix.[29] The timing and degree of collagen degradation is obscure. One author claims that collagen breakdown occurs during pregnancy without further changes during delivery,[123] but most reports describe significant decreases in cervical collagen content during labor.[58] These studies suggest that the cervical changes during parturition are a continuation of those that occur during pregnancy.[41] However, Rath et al. consider proteoglycan changes and, to a lesser extent, collagen remodeling as the cause of cervical ripening, whereas collagenolysis by specific catabolic enzymes, such as collagenase, is held responsible for the rapid dilatation of the cervix at parturition.[95]

In vitro measurements of compliance of cervical tissue obtained from women in labor are not available. Cervical behavior during labor has been studied by means of ultrasound cervimetry (chapter 3). The development of on-line soft ware for analysis of ultrasound cervimetry and intrauterine tocography, as described in chapter 6, holds a promise for future investigations into cervical dynamics.[128]

4.3 Mode of action of prostaglandins in the uterine cervix

Since the discovery of prostaglandins by Von Euler[131] the literature on these compounds has been growing exponentially. Although the derivatives of eicosanoic (20-carbon) polyunsaturated fatty acids are now usually called eicosanoids, the familiar term 'prostaglandins' will be used in this thesis for these locally active biochemical mediators released by cells on demand in response to appropriate chemical or physical stimuli. Prostaglandin-mediated effects on the uterus include induction and synchronisation of contractions, but the main effect on the cervix is ripening. It is beyond the scope of this chapter to present a detailed review of the physiology and pathophysiology of prostaglandin metabolism in human labor; excellent overviews have been published.[10,81] The discussion will be limited to an evaluation of what is known of the physiologic effects and biochemical mode of action of prostaglandins on the cervix during pregnancy and parturition.

Physiologic effects

Prostaglandins have been shown to affect many tissues and organs and to induce a broad array of functional responses.[83,84] They are local messengers synthesized and released from tissues on demand and they exert a locally confined action. Much of our knowledge regarding the physiologic properties of prostaglandins in cervical ripening are inferred from pharmacologic observations.[15] The ripening effect of intracervical,[5,80] intravaginal,[28,40,92,141] extraamniotic[17] and oral[52] administration of prostaglandins has been extensively applied in the termination of pregnancy in varying clinical conditions. Assessment of the specific bioactivity of prostaglandins is difficult because systemic measurements do not accurately reflect local synthesis and activity. First, highly active catabolic systems in lung, kidney and liver reduce the half-life of biologically active prostaglandins in the circulation. Second, prostaglandin production by platelets distorts findings in peripheral blood samples. Assessment of prostaglandin metabolites in urine samples or in amniotic fluid seems preferable,[54] but such measurements cannot distinguish between uterine and cervical production sites.

Most authors agree on a gradual increase in uterine prostaglandin production during the last weeks of pregnancy. Concentrations of PGE_2 and $PG\ F_{2\alpha}$ in amniotic fluid were shown to correlate directly with the cervical score in women at term who were not in labor.[14] At the onset of parturition there is a marked increase in the concentrations of $PG\ E_2$ and $PG\ F_{2\alpha}$ in amniotic fluid.[55,56] In labor progressing slowly or not at all, accumulation of prostaglandins occurs to a far smaller extent than in normally progressing labor.[96] Exogenously administered prostaglandins have been demonstrated to induce and shorten labor in patients with unripe[112] as well as ripe cervices.[121] There is evidence of a direct link between prostaglandins and increased cervical compliance.[31,87]

Biochemical mode of action

It is largely unknown how prostaglandins produce their effects on the cervix. It is unlikely that one single mechanism is reponsible for the wide variety of effects of prostaglandins, e.g. induction of uterine smooth muscle contractions and ripening of the cervix. Research is complicated by the fact that prostaglandins exhibit a highly organ and concentration dependent action.

Several biochemical mechanisms by which prostaglandins may act on the uterine cervix have been presented, but most are mainly hypothetical. All prostaglandins have specific binding sites, but little is known about the immediate post-receptor consequences of prostaglandin binding to their receptor sites.[101] Prostaglandins may act by regulating the c-AMP level and calcium metabolism of a target cell after binding to a specific receptor, thus eliciting prompt effects.[101] This model seems to fit the smooth muscle cell in particular. Prostaglandins could also act through enzyme induction. As an example of this mechanism, prostaglandin F_{2a} was shown to augment the activity of hyaluronic acid synthetase.[76] An interesting, but unproven, suggestion is that prostaglandins might cause a collagenolytic effect by attacking the interplay between collagen and proteoglycans.[126]

The target cells involved in cervical remodeling are leucocytes[51] and fibroblasts.[125] After treatment with prostaglandin E_2 fibroblasts showed signs of increased cellular activity, e.g. a fine granular loosening of the cytoplasm, vacuolised enlarged mitochondria and an increased number of cytoplasmatic vesicles close to the cell surface. The marked invasion of leucocytes into the cervix suggests that these cells participate in the widespread collagenolysis in the cervix found in intrapartum cervical biopsies.[51] Osmers et al. have shown that it is likely that the cells critically involved in collagen degradation during cervical dilatation are not resident fibroblasts but rather polymorphonuclear leucocytes emigrating from blood vessels.[86] Fibroblasts are claimed to be responsible for the changes in the proteoglycan pattern before parturition, whereas the main effect of leucocyte action would be collagenolysis during active labor.[95]

Prostaglandins and cervical dilatation

There could be three ways in which endogenous prostaglandins may bring about cervical changes. First, they could produce effects by inducing uterine contractions; second, they could promote collagen breakdown; third, they could induce changes in the glycosaminoglycan composition of the cervix.

Changes in cervical compliance at parturition seem to be independent of uterine activity.[115] This finding has been confirmed in experimental animal studies. Transsected sheep cervices have been shown to ripen in response to prostaglandins, which indicates that the presence of uterine activity, although problably helpful, is not a prerequisite of cervical ripening.[67]

The finding that PGE_2-treated cervices showed no augmented collagenase activity and no increase in the concentration of collagen breakdown fragments, compared to placebo-treated cervices, suggests that prostaglandins have no direct stimulatory effect on collagenase activity in vivo.[85,94]

The occurrence of changes in the glycosaminoglycan pattern combined with the ability of fibroblasts to produce hyaluronic acid synthetase after prostaglandin stimulation points to a relation between prostaglandins and the regulation of the glycosaminoglycan composition of the cervix.[11] In addition, the changes in glycosaminoglycans are likely to influence the mechanical strength of the collagen fibrils and make them more amenable to breakdown by proteolytic enzymes.[18]

4.4 Conclusion

In summary, cervical ripening is characterized by histochemical modification rather than breakdown of collagen and seems to be affected by prostaglandin-mediated fibroblast action that induces proteoglycan changes (fig. 4.3). The concept that collagen breakdown is the central issue in the cervical changes of pregnancy is currently under discussion and seems to apply less to the latent phase than to active labor. The collagenolytic changes during active labor, in particular during the acceleration phase, may reflect collagenase activity of leucocytes. The precise role of prostaglandins in this part of parturition is unclear. Cervical ripening, including the latent phase of labor, might mainly depend on a prostaglandin-induced change of cervical ground substance by fibroblasts, whereas active dilatation might be a result of collagenase activity of leucocytes. The subsequent activation of these two different physiologic mechanisms may explain the occurrence of the *acceleration point*, that is the sudden increase in cervical dilatation speed that characteristically occurs in advanced labor.[32] This concept, if true, provides a scientific rationale for treatment of a variety of clinical conditions, such as preterm labor and dystocia. It would be worthwhile to investigate the effects of prostaglandins on the cervix during labor in order to improve our understanding of cervical physiology and pathophysiology during parturition.

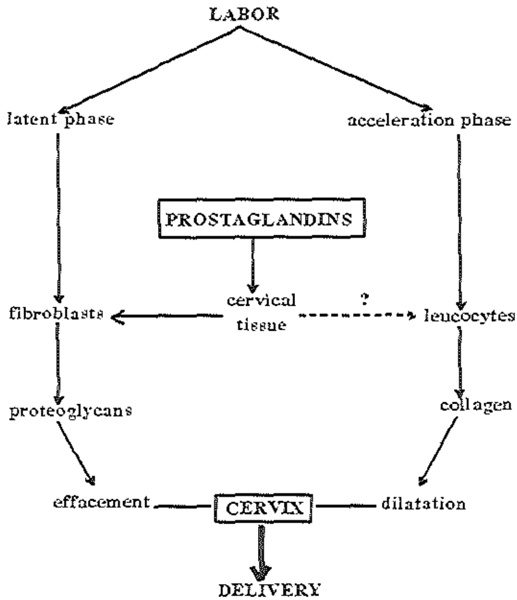

Figure 4.3. Schematic presentation of the putative role of prostaglandins in the cervical changes of pregnancy and labor.

Chapter 5

EFFECTS OF PROSTAGLANDIN E_2 GEL ON THE DYNAMICS OF THE UTERINE CERVIX DURING LABOR

5.1 Introduction

The efficacy of labor is determined to a large extent by the structure and behavior of the uterine cervix.[29] As outlined in chapter 3, ultrasound cervimetry is a valuable technique for the study of cervical behavior during labor. Using computer analysis, variables describing cervical dilatation and intrauterine pressure can be obtained. With regard to the changes in the cervix the *reaction point*, defined as the first occurrence of a cervical dilatation reaction during the course of labor, seems particularly interesting, as it may reflect structural changes in the cervix during the early latent phase of labor. As discussed in the previous chapter, the prostaglandins E_2 and $F_{2\alpha}$ contribute to the ripening of an unfavorable cervix, and to the achievement of efficient labor once cervical ripening has occurred.[47,65] Some reports indicate that collagen breakdown mainly occurs during the final part of pregnancy without further significant changes during parturition,[123] whereas others suggest that the process of cervical ripening continues during parturition, in particular during the latent phase of labor (chapter 4).[95] If the latter concept is true, local cervical application of prostaglandins during the latent phase of labor would be expected to facilitate cervical dilatation independent of uterine contractions, which would mean an earlier occurrence of the reaction and acceleration points.

In an attempt to adduce evidence to support or refute this concept, a randomized, double blind, placebo-controlled study was designed to determine the effects of locally applied prostaglandin E_2 gel on cervical behavior during labor. The gel was administered to two groups of 16 women each before and after the *reaction point*, respectively, and the differences in variables of cervical dynamics were assessed by on-line computer analysis of data, obtained by ultrasound cervimetry and intrauterine tocography.

5.2 Material and methods

The participants in the study were recruited from healthy nulliparous pregnant women under obstetric care in the antenatal clinic, who met the following criteria: 1. uncomplicated pregnancy of 38-42 weeks; 2. live fetus in cephalic presentation; 3. a reactive non-stress test at inclusion; 4. a cervical score according to Burnhill[9] of 6-8 and cervical dilatation not exceeding 3 cm; 5. informed consent after written and oral information.

Study protocol

On admission in early labor the first 16 women recruited for the study were randomly allocated to intracervical application of prostaglandin E_2 (dinoproston 0.5 mg in polydextrine gel, Cerviprost[R]) or matched placebo gels. The gel was applied immediately after the start of ultrasound cervimetry and intrauterine tocography using the commercially available catheter. In the next 16 women the same protocol was applied with the difference that the administration of the gels was delayed until immediately after the first cervical response to a myometrial contraction had been detected by on-line computer analysis of the uterine contraction and cervical dilatation signals. Labor was monitored as usual by the attending obstetrician. Randomization was carried out through the Clinical Trial Coordination Office of Organon International (Oss, The Netherlands). The study protocol was approved by the Research Review Board of the Westeinde Hospital.

Recording and data analysis

The technique of ultrasound cervimetry[27] in combination with intrauterine tocography has been described in detail in chapter 3. On-line analysis of the cervical dilatation and intrauterine pressure signals was applied as outlined in chapter 6. The following variables characterizing cervical dynamics were obtained: 1. the mean **cervical dilatation reaction**, defined as the mean gain in cervical dilatation during individual myometrial contractions (cm); 2. the time of the **reaction point**, defined as the first occurrence of a cervical dilatation reaction after the start of the recording (minutes); 3. the time of the **acceleration point**, which marks the end of the latent phase and the beginning of the acceleration phase of cervical dilatation and is determined by the value 0 in the third derivative of the dilatation signal (minutes); 4. the **dilatation time**, defined as the time between onset of recording and full dilatation (minutes); 5. the **contraction work**, estimated by the summation of the active pressure area of uterine contractions over the duration of the first stage of labor (kPa.s); 6. **mean contraction work**, calculated as the contraction work per hour of labor (kPa).

Statistical analysis

The code was broken after both parts of the study were finished. Data are presented as medians (range) throughout. Because the measured variables could not be accepted to follow a Gaussian distribution, Wilcoxon's rank-sum test was used to assess differences between groups. A p-value of 0.05 was taken as the level of statistical significance.

Table 5.1. Maternal age, cervical score according to Burnhill, gestational age and birthweight in the groups studied.

	gel before reaction point		gel after reaction point	
	PG E_2 (n = 8)	placebo (n = 8)	PG E_2 (n = 8)	placebo (n = 8)
maternal age (yr)	23 <20-30>	21.5 <18-30>	25 <20-28>	23 <18-26>
gestational age (wks)	39.5 <38.0-41.5>	40.0 <38.5-42.0>	40.5 <39.5-42.0>	40.0 <38.5-42.0>
cervix score	7 <6-8>	7 <6-8>	7.5 <6-8>	7.5 <6-8>
birthweight (g)	3575 <3080-4260>	3335 <2950-3775>	3200 <2590-3820>	3175 <2770-3440>

5.3 Results

Characteristics of the groups studied are shown in Tab. 5.1. No significant differences were found with regard to maternal age, cervical score at the start of recording, gestational age and birth weight. All women were delivered vaginally of healthy, live infants. Uterine hyperstimulation, defined as a persisting elevation of the uterine tone followed by fetal distress, was not encountered.

The cervical dilatation curves obtained in the four groups are presented in fig. 5.1. It should be noted that in the group of women treated before the reaction point, the start of the recording coincides with the application of prostaglandin E_2 gel or placebo, whereas this was not the case in the group treated after the reaction point. Asymmetric dilatation of the cervix causes small deviations in the diagonal alignment of the ultrasound transducers during labor, which explains why full dilatation is often measured as approximately 8 cm. In

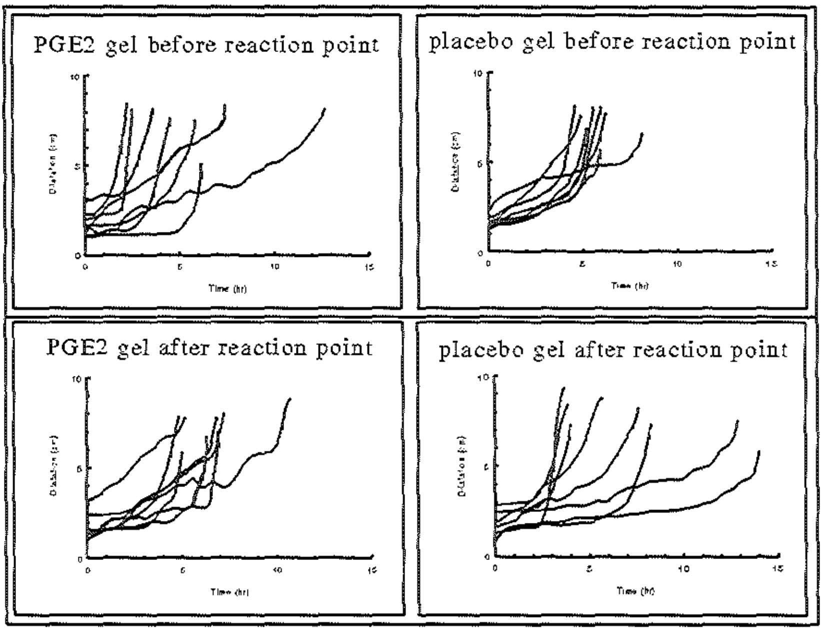

Figure 5.1. Partograms of women treated by PG E_2 or placebo gel before or after the reaction point (start recording: 0 h).

Table 5.2. Time intervals from start of recording to reaction and acceleration point, full dilatation and mean cervical dilatation reactions.

	gel before reaction point		gel after reaction point	
	PG E_2 (n = 8)	placebo (n = 8)	PG E_2 (n = 8)	placebo (n = 8)
reaction point (min)	34.5 <8-101>	40 <5-164>	-	-
acceleration point (min)	159.5 <113-490>	209.5 <102-450>	240.5 <109-450>	314 <172-756>
full dilatation (min)	310.5 <138-765>	346.5 <279-489>	397.5 <294-645>	400.5 <222-843>
mean cervical dilatation reaction (mm)	6 <3-8>	5.5 <4-9>	5 <3-12>	6 <3-12>

five women one or both ultrasound transducers became disconnected before full cervical dilatation was reached, but the recordings were of sufficient duration to be used for analysis.

In the women treated before the reaction point with prostaglandin E_2 gel, the reaction point, the acceleration point and the moment of full dilatation occurred earlier than in women treated by placebo gel, but the differences did not reach statistical significance (Tab. 5.2). The mean cervical dilatation reaction appears to be indentical in all the studied groups. The same applies for the differences in the times of the acceleration point and the moment of full dilatation in the women receiving gel after the reaction point.

Contraction work showed a large variability. Although it tended to be less in women who had received prostaglandin E_2 gel before the reaction point compared with placebo, no significant differences were demonstrated (Tab. 5.3).

Table 5.3. Contraction work and contraction work per hour.

	gel before reaction point		gel after reaction point	
	PG E_2 (n = 8)	placebo (n = 8)	PG E_2 (n = 8)	placebo (n = 8)
contraction work (kPa.s)	25.1 <10.5-107.2>	47.7 <34.4-92.5>	62.8 <35.0-92.3>	70.0 <28.9-104.0>
contraction work per hour (kPa)	7.3 <2.9-10.2>	8.0 <5.8-11.5>	8.8 <5.4-0.2>	8.9 <4.2-10.9>

5.4 Discussion

The assessment of the role of prostaglandins in the behavior of the cervix during the first stage of labor is hampered by difficulties in the determination of the local activity of prostaglandins and by problems associated with in vivo measurement of cervical changes.[119,128] The present study was designed to avoid both obstacles. Ultrasound cervimetry and intrauterine tocography were used in combination with on-line computer analysis, as outlined in chapter 6. In order to study the local effect of prostaglandins on the cervix prostaglandin E_2 gel was applied intracervically during physiologic labor. On-line detection of the reaction point was used to time the application of the gel in the second study group. As discussed in chapter 3, the reaction point reflects structural changes in the cervix during the early latent phase of labor. If local application of prostaglandins modifies the cervix during the early latent phase, the reaction point would be expected to occur earlier in the prostaglandin-treated women compared to placebo-treated subjects. If prostaglandins influence the cervix during the entire latent phase, an earlier occurrence of the acceleration point would be expected in those women receiving prostaglandin E_2 gel after the reaction point compared to those receiving placebo. Because no reaction point was demonstrable in multiparous women (chapter 3), nulliparous women were selected for the studies described in this chapter.

We noted a trend towards an earlier increase in cervical compliance after administration of prostaglandin E_2 gel considering the earlier occurrence of the reaction and acceleration points in women treated with prostaglandin E_2 gel before the reaction point. However, the differences between the prostaglandin and placebo-treated subjects in both groups were not statistically significant. The mean cervical dilatation reaction did not differ between prostaglandin and placebo treated women, indicating that cervical compliance is not altered by application of prostaglandin E_2 in physiologic labor. Also, no effect of administration of prostaglandins E_2 gel on the markers of the efficacy of labor, the duration of labor and the total and mean contraction work, was apparent.

Differences in methodology make our results difficult to compare to those obtained by others. Various methods have used in attempts to modulate the structure of the cervix in order to improve dilatation: the use of porcine relaxin;[142] cervical injections of hyaluronidase;[42] and vibration applied to the cervix.[48] None of these has been shown to influence cervical dilatation during normal labor. Most papers on the application of prostaglandins for obstetric purposes report on the induction of labor, usually in women with an unripe cervix.[92] Studies that include women with a ripe cervix compare the effects of prostaglandins with those of other methods, e.g. oxytocin administration[26] or to spontaneous labor.[65] This approach offers no information on the specific additional effect of prostaglandins in reducing cervical resistance.

In conclusion, the available evidence shows no evidently facilitating effect of prostaglandin E_2 gel application on cervical behavior, when administered during physiologic labor in nulliparous women. Apparently, the prostaglandin-mediated structural changes of the cervix occur before the start of labor. The effects of prostaglandins on cervical dystocia remain to be investigated.

Chapter 6

ON-LINE COMPUTER ANALYSIS OF CERVICAL DILATATION AND INTRAUTERINE PRESSURE DURING HUMAN LABOR

6.1 Introduction

Using off-line computer analysis of data obtained by a combination of ultrasound cervimetry and simultaneous measurement of intrauterine pressure, it was shown in chapter 3 that cervical dilatation follows a typical course with the *reaction point* and *acceleration point* as characteristic landmarks. These points reflect structural changes in the cervix during parturition. In order to study the physiologic processes in the cervix that control cervical dilatation during labor, a research protocol was developed that involved the application of prostaglandin E_2 gel during labor before and after the reaction point (chapter 5). This requires on-line computerized detection of the reaction point during labor. This chapter reports the development of a software package that performs a full on-line analysis of cervical dilatation and intrauterine pressure signals, thus providing the necessary data for the research protocol described in chapter 5.

6.2 Problems and general approach

The electrical outputs of a *cervimeter* and a *tocograph*, measuring cervical dilatation signals and intrauterine pressure, respectively, are sampled. The analysis of the signals requires the detection of uterine contractions and cervical dilatation reactions. The results of the basic analysis can be used for the determination of the reaction and acceleration points, the time and contraction work needed to reach full dilatation, and the gain in cervical dilatation during single uterine contractions.

The intrauterine pressure signal has a constant resting level with episodic elevations during contractions (Fig. 6.1). The shape of the cervical dilatation signal is similar with the exception that the baseline is steadily rising as labor progresses. Therefore, both signals can be considered as a series of comparable segments, each segment consisting of a resting period of variable

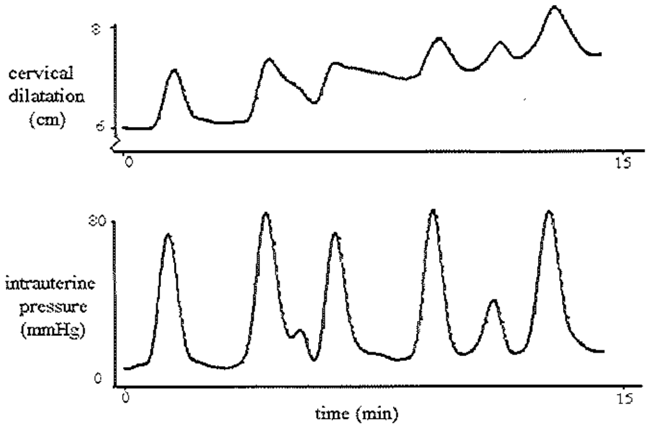

Figure 6.1. Cervical dilatation (top) and intrauterine pressure (bottom) . Note the gradual rise of the cervical dilatation baseline.

duration followed by an elevation phase, called *wave*. Each wave is primarily characterized by its *beginning, maximum and end.* These *reference points* can be determined using the first time derivative of the pressure and dilatation signal (see paragraph 6.5.). However, in practice this detection method is hampered by the many rapid changes in the first derivative, caused by high-frequency noise in the original signal (fig. 6.2). The average power spectrum of the noise shows a broad bandwidth compared to the slowly varying signals, so a low pass filter should be used to increase the signal-to-noise ratio. A differentiating filter then allows the detection of the reference points defined above and an appropriate algorithm enables further on-line analysis of both signals and their interrelationship.

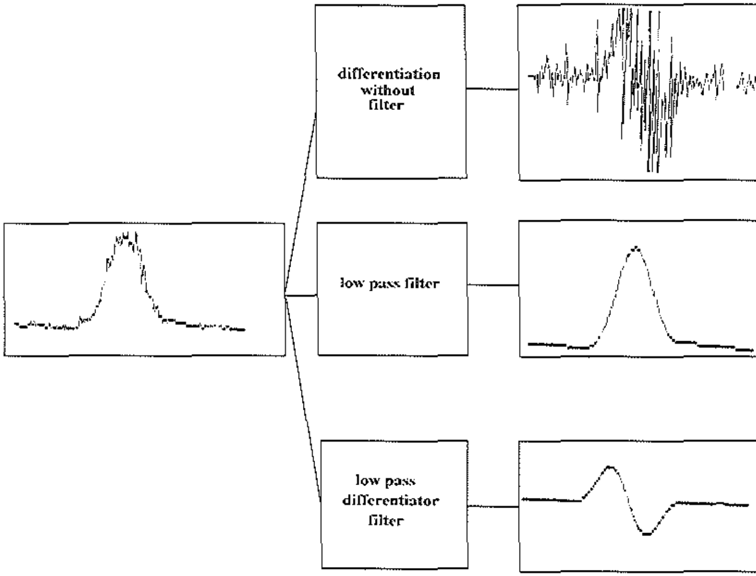

Figure 6.2. Left panel: original signal, right panels: differentiated and filtered signals.

6.3 Data acquisition and storage

Measurement of intrauterine pressure is performed by a fluid-filled open tip catheter connected to the pressure transducer of a standard tocograph (Hewlett-Packard 80300A). The catheter is inserted into the uterus through the vagina and cervix after rupture of the membranes. The output signal is an electrical representation of the intrauterine pressure.

Cervical dilatation is assessed by means of a custom-made ultrasound cervimeter.[27] This cervimeter consists of two spiral-shaped ultrasound transducers screwed into the opposing rims of the dilating cervix. A 0.6 MHz signal burst is generated with a 200 Hz repetition frequency by one transducer and detected by the opposite one. The distance Δl between the transducers, representing cervical dilatation, is described by

$$\Delta l = v \cdot \Delta t \quad (1)$$

in which v is the ultrasound velocity (approximately 1500 m/s in all tissues involved[60] and Δt the travelling time of a pulse between the transducers. The output voltage of the equipment is proportional to Δt and is thus a measure of Δl. The original dilatation and intrauterine pressure readings are written on the two channel polygraph of the tocograph and simultaneously digitized at a sampling rate of 1 Hz by a 16-bit RTI 815-Multifunction Input/Output Board (Analog Devices) in an 80X86-based personal computer programmed in Turbo Pascal 5.0[®]. In order to allow subsequent on-line analysis the sampling and storage of the digitized signals is interrupt-driven. The raw and analyzed data are stored on hard disk and displayed on the computer screen.

6.4 Data filtering

The similarity of the pressure and dilatation signals allows the use of the same filtering and analysis algorithm. Because of the low frequencies involved, digital instead of analogous filtering is used. To avoid the accumulation of errors and output delays of low pass filtering with subsequent differentation, a differentiating digital filter with low pass characteristics was developed. The ideal transfer function $G^*(\omega)$ for this type of filter with cut-off frequency ω_s/B is:

$$G^*(\omega) = \begin{cases} j\omega & (\omega \leq \frac{\omega_s}{B}) \\ 0 & (\frac{\omega_s}{B} < \omega < \frac{\omega_s}{2}) \end{cases} \quad (2)$$

where: $\omega = 2\pi f$ (f = frequency)
$\omega_s = 2\pi f_s$ (f_s = sampling frequency)
and $B > 2$.

The coefficients g_n for the non-recursive (finite-duration impulse response) digital filter which is optimal in the least integral square error's sense can be computed using the Fourier series method:[118]

$$g_n = \frac{1}{\omega_s}\int_{\frac{-\omega_s}{B}}^{\frac{\omega_s}{B}} j\omega e^{(j\omega nT)} d\omega$$
$$g_0 = 0 \tag{3}$$
$$g_{-n} = -g_n$$

where: n = coefficient number (n > 0)
T = $2\pi/\omega_s$
j = imaginary unit

Since signal sampling is performed at a 1 Hz rate (ω_s=2π rad/s), Eq. 3 reduces to:

$$g_n = \frac{2}{nB}\cos(\frac{2\pi n}{B}) - \frac{1}{\pi n^2}\sin(\frac{2\pi n}{B})$$
$$g_0 = 0 \tag{4}$$
$$g_{-n} = -g_n$$

In order to approach the ideal transfer function described in Eq. 2 as closely as possible, all positive integer values of n should be included in the computations. In practice, however, the Fourier series has to be truncated to minimize computing time. In general, a truncated Fourier-series tends to have excessive ripples near the points where $G^*(\omega)$ has sharp jumps, even though it is best in the least integral square error's sense. The ripple, known as Gibbs' phenomenon.[118] becomes more prominent when the number of filter coefficients, or *taps*, is decreased. Reduction of the Gibbs' phenomenon can be achieved by a window function at the cost of a broadening of the transition zone near the cut-off frequency. For the present application truncation at n = 60 in combination with a Hamming-window with coefficients h_n

$$h_n = 0.5*(1+\cos(\frac{2\pi n}{N})) \tag{5}$$

proved a reasonable trade-off, resulting in a 121 tap filter with a delay of 60 seconds between the input and output signal. A cut-off frequency of 0.03 Hz (B = 33) turned out to be optimal for both signals. A lower cut-off frequency results in decreased maxima in the filtered signals, whereas higher cut-off frequencies did not improve the signal-to-noise ratio sufficiently. In this way the points of time, at which reference points are reached, were assessed reliably. The corresponding value of intrauterine pressure or cervical dilatation was obtained after elimination of noise effects by low pass filtering with the same cut-off frequency of 0.03 Hz. The ideal response of this filter is:

$$G^*(\omega) = \begin{cases} 1 & (|\omega| \leq \frac{2\pi}{33}) \\ 0 & (\frac{2\pi}{33} < |\omega| < \pi) \end{cases} \tag{6}$$

The filter coefficients, determined by the same Fourier series and Hamming window method,[118] are given by:

$$\begin{aligned} g_n &= \frac{1}{\pi n}\sin\left(\frac{2\pi n}{33}\right)\cdot\left(1+\cos\left(\frac{2\pi n}{33}\right)\right) \quad (1 \leq n \leq 60) \\ g_0 &= \frac{2}{B} \\ g_{-n} &= g_n \end{aligned} \tag{7}$$

In order to determine the acceleration point a smoothed partogram curve is obtained by low pass filtering of the dilatation signal with a cut-off frequency of 0.001 Hz (Eq. 7).

6.5 Data analysis

The cervical dilatation waves can be divided into four types. Most waves, referred to as *standard waves*, are characterized by a monotone rise and fall (Fig. 6.3). *Shifts* consist of isolated rises or falls in pressure or dilatation (Fig. 6.3b). *Composite slope waves* have (multiple) bending points, but a single maximum (Fig. 6.3c). *Camel waves* contain multiple maxima (Fig. 6.3d).

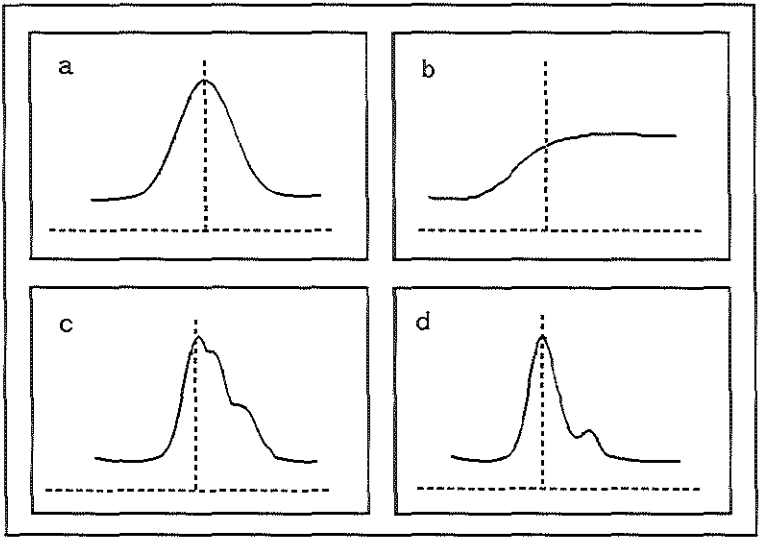

Figure 6.3 The various wave types.

Fig. 6.4 shows the algorithm that classifies the detected waves. Basically, the slopes of each wave are subdivided into a sequence of rising or falling sections. A section is demarcated by the time interval in which the absolute value of the first derivative of the original signal exceeds the empirically determined values of 0.2 mmHg/s for pressure P, or 0.007 cm/s for dilatation D, respectively. As long as the sign of the first derivative *dD/dt* or *dP/dt* does not change, the consecutive sections are considered to form one slope provided that the time between the end of one section and the start of the next one does not exceed the empirically determined waiting time t_{w1} = 80 s. A wave starting with a falling slope is a negative shift. When a wave starts with a rising slope without a subsequent falling slope within the empirically determined waiting time t_{w2} = 40 s it is called a positive shift. Camel waves are detected when two consecutive waves fall within t_{w2} and have at least a difference of 5 mmHg or

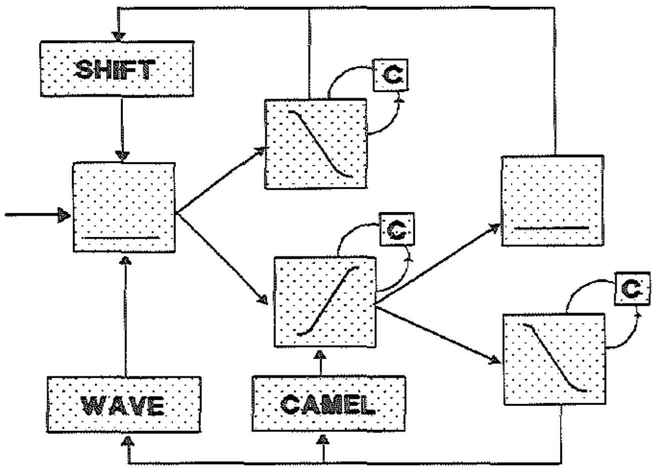

Figure 6.4. Basic algorithm of analysis,showing the detection principle of SHIFT, CAMEL, C(omposite) and (standard) WAVE.

0.25 cm in starting levels. In the event of a slope consisting of multiple sections, a composite-slope wave is identified, whereas a standard wave is detected in all other cases.

Separate data storage for intrauterine pressure and cervical dilatation is performed per segment, consisting of a signal fragment from the end of a wave or shift to the end of the next one. This segment data record contains the wave characteristics: shift, standard wave, camel wave, or composite-slope wave with the corresponding number of positive and negative sections. The data record also holds the wave reference points, beginning, maximum and ending, with corresponding values of pressure and dilatation. Additionally the mean resting levels of pressure and dilatation and the time between begin and end of a wave are recorded. The segmental data storage record is completed with the integrated height of each wave together with the squared integrated difference between the original and filtered signals. The latter is a measure of the amount of the high frequency energy that is filtered away. This proved a reliable determinant for the detection of active pushing efforts by the patient. The dilatation data are validated by eliminating those dilatation waves that are not generated by contractions according to the criteria explained in Table 6.1. The results of the basic analysis described above constitute the material for further processing in

Table 6.1. Validation criteria for detection of pressure and dilatation wave couples.

1*	the pressure wave starts before the corresponding dilatation wave
2*	the maximum of the pressure wave occurs after the beginning of the corresponding dilatation wave
3*	the maximum of the dilatation wave occurs within 20 sec of the maximum of the corresponding pressure wave
4*	the maximum of the dilatation wave occurs before the end of the corresponding pressure wave

order to obtain clinically useful information. The reaction point is detected at the beginning of the first sequence of three consecutive validated cervical reactions. This precludes the erroneous detection of a reaction point when a pressure wave is accidently associated by a gain in cervical dilatation. Additional low pass digital filtering of the cervical dilatation signal with a cut-off frequency of 0.001 Hz was used to obtain a smoothed cervicograph curve. The point of maximum concavity in the partogram represents the acceleration point and is represented by a zero transition from positive to negative of the third derivative of the low pass filtered dilatation signal. This third derivative was computed for every i^{th} sample using:

$$\frac{d^3y(i)}{dt^3} = -\frac{1}{2}y(i-2) + y(i-1) - y(i+1) + \frac{1}{2}y(i+2) \qquad (8)$$

where $y(i)$ is the i^{th} sample of the low pass filtered dilatation signal. The mean **cervical dilatation reaction** was defined as the mean gain in cervical dilatation during individual myometrial contractions (cm) and was calcutated by determining the mean difference between the begin and maximum dilatation of all validated cervical dilatation reactions. The **contraction work** was estimated by summing up the active pressure areas of all uterine contractions over the duration of the first stage of labor. The **mean contraction work** was then calculated as the contraction work divided by the number of hours of labor.

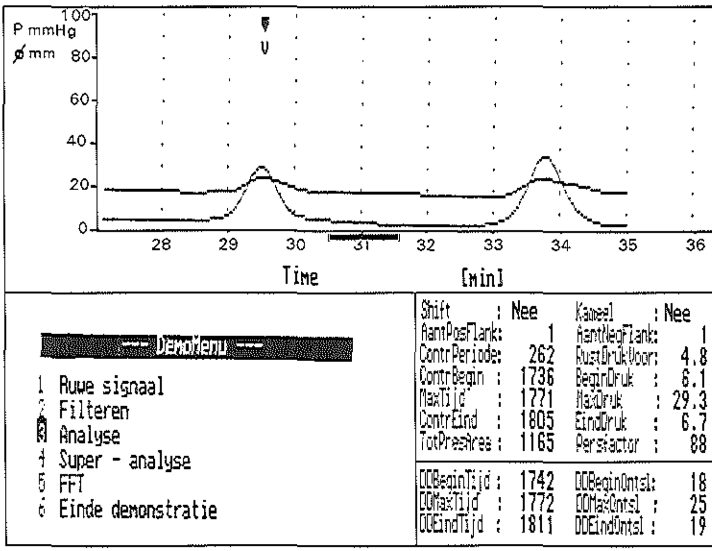

Figure 6.5. Computer screen display during recording. The top panel shows the filtered signals. At the bottom right numerical data of the analyzed signals is displayed.

6.6 Practical applications

During labor the computer screen continuously displays the cervical dilatation and pressure signals (fig. 6.5). Simultaneously the analyzed data of each contraction and cervical dilatation reaction are displayed. Data can be displayed graphically, e.g. partograms, or plots of cervical dilatation against cumulative contraction work (fig. 6.6).

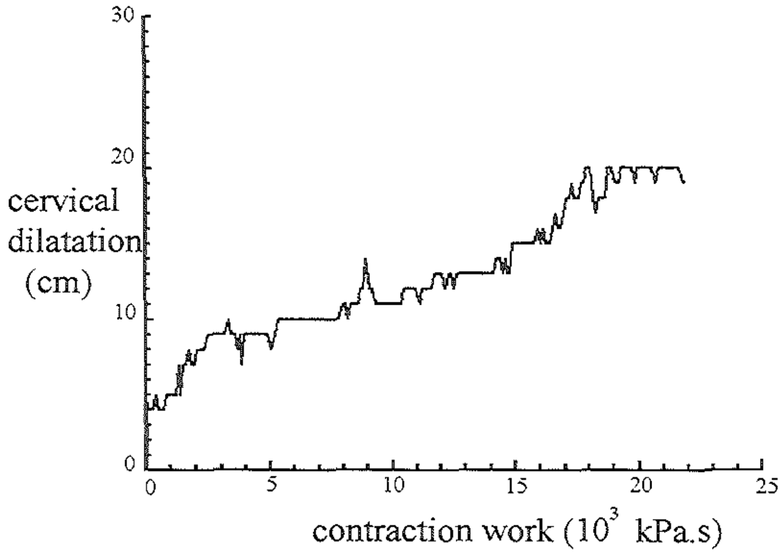

Figure 6.6. Cervical dilatation against contraction work in a nulliparous woman.

Computer-aided ultrasound cervimetry combined with intrauterine tocography allows clinical and scientific applications. The clinical benefits include replacement of pelvic examinations, which can be uncomfortable and painful for the woman in labor. Continuous monitoring of cervical dilatatation might be helpful in monitoring women at risk for premature delivery. An automatic alarm in case of progression of cervical dilatation is technically feasible. The on-line analysis of the cervical dilatation and intrauterine pressure signals allows an objective diagnosis of labor arrest. As the arrest of labor is the single factor that has contributed most to the increase in cesarean deliveries,[7] standardized criteria for this diagnosis might be helpful in lowering the number of cesarean sections. However, the opportunities for investigations into the physiology of the cervix during labor probably outweigh the clinical benefits. In particular, pharmaceutical intervention studies in which cervimetry is used to determine the time and effect of the medication could be worthwhile. Another field of interest is the evaluation of various drugs used to stimulate uterine contractions and the fine tuning of their dosage schemes.

Chapter 7

GENERAL CONCLUSIONS

The aim of the present thesis was to investigate the behavior of the uterine cervix during the first stage of labor. In order to study cervical behavior, a method for reliable assessment of cervical dilatation in relation with intrauterine pressure had to be identified and evaluated. In a review of the literature ultrasound cervimetry emerged as the most promising method available for the study of cervical behavior during labor. Using this method in nulliparous and parous women in labor, cervical dilatation patterns were continuously assessed. Cervical dilatation was found to follow a typical course, that is comparable to the sigmoid-shaped curve, based on digital cervimetry, with the exception that a deceleration phase was never observed. Analysis of the obtained data strongly suggested the occurrence of structural cervical changes during labor. Nulliparous labor was found to be characterized by a reaction point, at which the cervix starts to react at myometrial contractions during the early latent phase of labor. This finding indicates an augmentation of cervical elasticity. The cervical dilatation curves were characterized by an acceleration point, which again suggests that structural changes occur in the cervix during the first stage of labor.

Prostaglandins are known modulators of cervical function during pregnancy, but detailed knowledge about their specific role during cervical dilatation is scarce. A hypothetic model was developed on the basis of the available literature. In this model the latent phase of labor was considered to be the last part of the phase of cervical ripening and to depend on prostaglandin-induced changes of the cervix, probably alterations in the cervical ground substance. On the other hand, active dilatation was considered to be a result of collagenase dependent cervical changes, possibly reflecting the activity of leucocytes. This model was tested by comparing the effects of intracervical application of placebo and prostaglandin gels during labor. For that purpose the gels were administered before or after the reaction point and the differences in cervical behavior were assessed by computer-aided analysis. No evident effects werenoted, leading to the conclusion that apparently the prostaglandin-mediated changes of the cervix are completed at the beginning of labor. The latent phase of labor cannot be considered to be merely an extension of cervical ripening.

SUMMARY

This thesis consists of 6 chapters dealing with various aspects of prostaglandins and cervical dynamics during labor.

CHAPTER 1 is a brief introduction describing the background and the objectives of the reviews and investigations presented in this thesis. The main questions to be addressed are the usefulness of ultrasound cervimetry as a tool for the study of cervical behavior during parturition, and the role of prostaglandins in the control of the cervix during the first stage of physiologic labor.

CHAPTER 2 reviews the various techniques used for assessment of cervical dilatation during labor or 'cervimetry', including digital, (electro)mechanical, electromagnetic and ultrasound cervimetry. The validity and usefulness of instrumental cervimetry is assessed on the basis of the available literature. Cervimetry using ultrasound transducers allows continuous and reliable recording of cervical dilatation during labor with little discomfort to the patient. In comparison with other instrumental techniques for measurement of cervical dilatation ultrasound cervimetry seems to be the most promising method available.

CHAPTER 3 presents a study in which cervical dynamics during the first stage of labor were assessed by a combination of ultrasound cervimetry and intrauterine tocography. Sixty-two parturients were divided into four groups: nulliparous women in spontaneous (n = 9) or oxytocin-induced labor (n = 26), parous women in spontaneous (n = 11) or oxytocin-induced labor (n = 16). Intrauterine pressure and cervical dilatation were continuously recorded and assessed by off-line computer analysis.

All women with spontaneous labor showed cervical responses to uterine contractions at the beginning of the recording. The first cervical response to a uterine contraction occurred at significantly smaller dilatation in parous than in

nulliparous women with induced labor (2.9 and 3.6 cm, respectively). Also acceleration of cervical dilatation occurred at less dilatation in parous than in nulliparous women (3.4 cm and 4.8 cm, respectively), and myometrial work per cm of cervical dilatation was less in parous than in nulliparous parturients.

The results indicate significant differences between cervical dilatation patterns in nulliparous and parous women, which may be due to structural cervical changes caused by labor and parturition.

CHAPTER 4 explores the relationship between prostaglandins and the control of cervical behavior. The histological, biochemical and biophysical characteristics of the cervix before and during pregnancy and during labor are reviewed, followed by a discussion of what is known about the mode of action of prostaglandins on the cervix. Cervical ripening is characterized by histochemical modification rather than breakdown of collagen and seems to be affected by prostaglandin-mediated fibroblast action that induces proteoglycan changes. The concept that collagen breakdown is the central issue in the cervical changes of pregnancy is currently under discussion and seems to apply less to the latent phase than to active labor. The collagenolytic changes during active labor, in particular during the acceleration phase, may reflect collagenase activity of leucocytes. The precise role of prostaglandins in this part of parturition is unclear. Cervical ripening, including the latent phase of labor, might mainly depend on a prostaglandin-induced change of cervical ground substance by fibroblasts, whereas active dilatation might be a result of collagenase activity of leucocytes. It is concluded that it would be worthwhile to investigate to what time and extent prostaglandins exert an effect on the cervix during labor in order to improve our understanding of cervical physiology and pathophysiology during parturition.

CHAPTER 5 presents an investigation into the effects of prostaglandin E_2 gel on the dynamics of the uterine cervix during labor by means of computer-aided ultrasound cervimetry and intrauterine tocography.

Thirty-two parturients were randomly assigned to intracervical application of prostaglandin E_2 or placebo gel during labor in a double blind fashion. In the first group of 16 women the gel was applied at the onset of labor, in the second group of 16 women after the reaction point, defined as the occurrence of the first cervical response to myometrial contractions. The following variables determined by on-line analysis of data obtained by ultrasound cervimetry and intrauterine tocography were analyzed: the reaction and acceleration point, the mean cervical dilatation reaction, the dilation time and the mean and total contraction work.No significant differences could be demonstrated with regard to the investigated variables between the prostaglandin and placebo-treated subjects in both groups. The results indicate that prostaglandins administered during physiologic labor do not augment cervical compliance. Apparently, the prostaglandin-mediated changes of the cervix are completed at the beginning of labor.

CHAPTER 6 describes a new method for on-line digital filtering and analysis of cervical dilatation and intrauterine pressure signals during labor. The similarity of the pressure and dilatation signals allows the use of one filtering and analysis algorithm for both, based on the first and third time derivative. In order to allow subsequent on-line analysis the sampling storage of the digitized signals was interrupt-driven. To avoid the accumulation of errors and output delays of low pass filtering with subsequent differentation, a differentiating digital filter with a cut-off frequency of of 0.03 Hz was developed. A smoothed partogram curve was obtained by additional low pass filtering of the dilatation signal with a cut-off frequency of 0.001 Hz. The four types of dilatation and pressure waves, standard waves, shifts, composite-slope waves and camel waves, were detected by an appropriate algorithm. Basically, the slopes of each wave were subdivided in a sequence of rising and falling sections. A section is demarcated by the time interval in which the absolute value of the first time derivative of the original signal exceeds the empirically determined values of 0.2 mmHg/s for pressure or 0.007 cm/s for dilatation, respectively. The results of the basic analysis constitute the material for further processing in order to extract useful information, such as the reaction and acceleration point.

SAMENVATTING

Dit proefschrift bestaat uit 6 hoofdstukken waarin verschillende aspecten worden behandeld van de veranderingen van de cervix tijdens de baring en in het bijzonder de rol die prostaglandines hierin spelen.

HOOFDSTUK 1 geeft een korte inleiding, waarin de achtergronden en doelstellingen worden beschreven van de in dit proefschrift gepresenteerde literatuurstudies en onderzoeken. Met name wordt gekeken naar de bruikbaarheid van ultrasone cervimetrie gecombineerd met intrauteriene tocografie voor de studie van het gedrag van de cervix uteri tijdens de baring. Tevens zal de invloed van prostaglandines op het gedrag van de cervix tijdens de ontsluitingsfase van de baring bestudeerd worden.

HOOFDSTUK 2 behandelt de verschillende technieken die in de literatuur zijn beschreven om de ontsluiting van de cervix tijdens de baring te meten. Voor deze zogenaamde 'cervimetrie' zijn naast het vaginaal toucher vooral (electro)mechanische, electromagnetische en ultrageluidstechnieken gebruikt. De validiteit en bruikbaarheid van de verschillende vormen van instrumentele cervimetrie wordt aan de hand van de gevonden literatuur bepaald. De cervimeters, waarbij gebruik gemaakt wordt van aan de cervix bevestigde ultrageluids-transducers, lijken verhoudingsgewijs het best bruikbaar en tevens het patiënt-vriendelijkst te zijn.

HOOFDSTUK 3 omvat een onderzoek naar de dynamische eigenschappen van de cervix tijdens de ontsluiting door middel van ultrasone cervimetrie en intra-uteriene tocografie. 62 patiënten werden onderverdeeld in vier groepen: nulliparae met spontaan begonnen baring (n = 9), nulliparae na oxytocine-inleiding van de baring (n = 26), multiparae met spontaan begonnen baring (n = 11) en multiparae na oxytocine-inleiding van de baring (n = 16). Intra-uteriene druk en ontsluiting werden continu gemeten en naderhand met de computer geanalyseerd.

Alle vrouwen met spontaan begonnen baring bleken reeds een op de weëen reagerende cervix te hebben bij het starten van de registratie. In de ingeleide groep bleek dat bij multiparae de cervix bij een geringere mate van ontsluiting begint te reageren vergeleken met nulliparae (3.4 en 4.8 cm respectievelijk). De hoeveelheid arbeid per centimeter ontsluiting was bij multiparae ook minder dan bij nulliparae.

Op basis van deze resultaten wordt geconcludeerd dat er aanzienlijke verschillen zijn tussen nulliparae en multiparae wat betreft het ontsluitingspatroon. Deze zouden kunnen berusten op structurele veranderingen van de cervix tijdens de baring. De techniek van ultrasone cervimetrie, gecombineerd met meting van intra-uteriene druk, bleek goed te bruikbaar voor het bestuderen van de dynamische eigenschappen van de cervix tijdens de baring.

HOOFDSTUK 4 is gewijd aan de relatie tussen prostaglandines en het gedrag van de cervix tijdens de baring. De histologische, biochemische en biofysische eigenschappen van de cervix voor en tijdens de zwangerschap en tijdens de baring worden besproken, gevolgd door een literatuurstudie naar de specifieke rol van prostaglandines in de cervix. Het rijpen van de cervix onder invloed van prostaglandines lijkt meer door een histologische herstructurering dan door absolute afbraak van collageen bepaald te worden. Fibroblasten spelen hierin een belangrijke rol. Tijdens de actieve ontsluitingsfase staat collageenafbraak onder invloed van collagenase dat door leucocyten geproduceerd wordt centraal. De rol van prostaglandines in dit gedeelte van de baring is onduidelijk. Op grond van de resultaten van deze literatuurstudie lijkt het veelbelovend om te onderzoeken tot wanneer en in welke mate prostaglandines een effect hebben op de cervix tijdens de ontsluiting. Een dergelijk onderzoek zou het inzicht in de (patho)fysiologische processen van de cervix tijdens de baring vergroten.

HOOFDSTUK 5 bespreekt een onderzoek naar de effecten van prostaglandine E_2 gel op de dynamische eigenschappen van de cervix tijdens de baring door middel van gecomputeriseerde ultrasone cervimetrie en intra-uteriene tocografie.

Aan 32 vrouwen werd gerandomiseerd en dubbel-blind prostaglandine E_2 of placebo gel intracervicaal toegediend tijdens de baring. Aan de eerste 16 barenden werd de gel toegediend bij het begin van de baring, wanneer de registratie werd begonnen. De tweede groep van 16 barenden kreeg de gel direct na het reactiepunt, gedefinieerd als het optreden van de eerste cervicale reactie op een contractie. De bepaalde parameters waren: het reactie- en acceleratiepunt, de gemiddelde ontsluitingsreactie en de tijd en de totale hoeveelheid arbeid om volledige ontsluiting te bereiken.

Er werden geen significante verschillen gevonden tussen de met prostaglandine E_2 gel en de met placebo gel behandelede barenden, noch in de vóór, noch in de ná het reactiepunt behandelde groep.

De resultaten wijzen uit dat de toediening van prostaglandines tijdens fysiologische baringen geen duidelijke veranderingen in de dynamische eigenschappen van de cervix teweeg brengt. Blijkbaar zijn de door prostaglandines geïnduceerde veranderingen van de cervix in fysiologische omstandigheden op dat tijdstip voltooid.

HOOFDSTUK 6 beschrijft een nieuwe methode voor het on-line digitaal filteren en analyseren van de door middel van ultrasone cervimetrie en intra-uteriene drukmeting verkregen gegevens. De gelijkvormigheid van druk- en ontsluiitingssignaal staat toe dat er één algoritme wordt gebruikt voor het filteren en de analyse van beide. Het verzamelen en opslaan van de meetgegevens is interrupt-gestuurd, zodat on-line analyse in de resterende tijd mogelijk is. Een digitaal differentiërend filter met een afsnijdfrequentie van 0.03 Hz voorkomt dat een opeenstapeling van output-vertragingen ontstaat. Het analyse-algoritme detecteert vier verschillende vormen van weeën (en gezien de gelijkvormigheid dus ook cervicale ontsluitingsreacties): de normale weeën, "shifts", samengestelde weeën en kameleweeën. De hellingen van deze weeën bestaan uit een serie van dalende en stijgende deelhellingen. Een deelhelling wordt in de tijd begrensd door de absolute waarde van de eerste afgeleide van het signaal, die voor de intrauteriene boven de empirische waarde van 0.2 mmHg/s moet liggen en voor de ontsluiting boven de 0.007 cm/s. De geanalyseerde data worden per segment opgeslagen, waarbij een segment loopt van het begin van een wee of ontsluitingsreactie tot het begin van de volgende. De gegevens van de basisanalyse worden on-line bewerkt om bruikbare informatie, zoals het reactie- en acceleratiepunt, te verkrijgen.

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