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ELECTRICAL IMPEDANCE MEASUREMENTS OF THE

UTERINE CERVIX IN PREGNANCY

BEING

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BY

MICHAEL PATRICK O'CONNELL

MB BCH BAO DCH (NUI) MRCOG

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SUPERVISER: MR STEPHEN W LINDOW

SENIOR LECTURER IN PERINATOLOGY

UNIVERSITY OF HULL

HEAD OF DEPARTMENT: PROFESSOR STEPHEN R KILLICK

PROFESSOR OF REPRODUCTIVE MEDICINE AND SURGERY,

UNIVERSITY OF HULL

DEDICATED TO

My wife Emer and daughters Aisling and Cliodhna

CONTENTS

CHAPTER 1 LITERATURE REVIEW

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

A.C	Alternating Current
A.ms	Amps per millisecond
CIN	Cervical intra-epithelial neoplasia
ε	Permittivity
ε^*	Complex permittivity

ε_s	Permittivity at a very low frequency
ε_∞	Permittivity at a very high frequency
E	Electric field
EI	Electrical impedance
EIT	Electrical impedance tomography
F	Faraday
GAGS	Glycosaminoglycans
Hz	Hertz
I	Current
IEC	International electrotechnical commission
IVF	*In-vitro* fertilisation
j	Orthogonal direction
μA	Micro amps
mA	Milli amps
mg	Milligrammes
mHz	Milli hertz
MHz	Mega hertz
MRI	Magnetic resonance imaging
ρ	Resistivity
PG	Prostaglandin
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PGI_2	Prostaglandin I_2
R	Extracellular resistivity

r^2	Pearson correlation co-efficient
ROC	Receiver operator curve
S	Intracellular resistivity
τ	Relaxation time
Ω	Ohm
Ω.m	Ohm metres
ω	Angular frequency
V	Volts
Z	Impedance

SUMMARY OF THE THESIS

INTRODUCTION

The role of the cervix in pregnancy is enigmatic. The characteristics of the cervix permit it to carry out its vital but conflicting functions of acting as a mechanical barrier to retain the conceptus during pregnancy, ripening prior to labour and to allow the uterine contractions to effect dilatation at an appropriate time for the conceptus to be expelled.

Avis et al (1996) reported the results of a pilot study to measure the *in-vitro* electrical impedance of samples of cervix taken at Caesarean section from six patients at various stages within the third trimester of pregnancy.

In the study a sample of the cervix was excised from the upper segment of the cervix at Caesarean section after delivery of the baby. Eleven patients were initially recruited but data was only obtained from six. Of the six patients two underwent emergency Caesarean section following the onset of labour. The remaining four patients underwent elective Caesarean section.

The electrical impedance of the cervical sample was measured over a range of frequencies using a single channel multi-frequency impedance measuring system utilising a four electrode method.

The data was normalised using the lowest frequency measurement as the reference and the normalised impedance values were fitted to the Cole equation (Cole and Cole 1941).

The subjects were divided into term ($\geq$ 38weeks) and preterm ($<$ 37weeks). The ratio of extracellular to intracellular space (R/S) decreased with increasing gestation possibly indicating an increasing extracellular space in the term group.

This was explained in part by an increase in cervical hydration with increasing gestation.

The aim of this work was to characterise the cervix and its change in pregnancy using electrical impedance measurements in the *in-vivo* setting.

PATIENTS AND METHODS

The local research ethics committee granted approval for each of the studies reported in this thesis and written informed consent was obtained from each patient prior to entry into the study (Appendix 1-3). Patients were recruited from the antenatal wards, the antenatal clinic, the delivery suite, the post-natal wards, the post-natal clinic and the non-pregnant were recruited from the colposcopy clinic in Sheffield.

Transfer impedance measurements were made at a frequency of 4.8kHz using a 5.5mm and 8mm diameter pencil probe, with four gold electrodes mounted flush with the face of the probe. The probes were placed on the surface of the cervix and did not enter the substance of the cervical tissue. A current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential was measured between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the average calculated. The equipment was calibrated before each set of results by placing the probe in saline solutions with a range of concentrations and hence electrical resistivities. The in-vivo results are thus presented in units of Ohm metres (Ωm).

In all 200 pregnant women participated in the various studies. Initially methodological studies looking at inter-observer, intra-observer and effect of the

site where the probe was place on the cervix were performed. The effect of parity, gestational age, and maternal age was investigated. In comparing the non-pregnant and pregnant cervix we used data from the colposcopy clinic in Sheffield for the non-pregnant group. The induction of labour studies investigated electrical impedance measurements compared to Bishop scoring of the cervix. We assessed the effects of prostaglandin on the electrical impedance readings

The post-partum study aimed to assess the remodelling process of the cervix post delivery.

Finally we performed a survey of patients attitudes to the investigations.

Results

The inter-observer study demonstrated large variability between individual readings but the variability was much improved when mean readings were used for analysis. This improved significantly once a plateau was reached on the learning curve.

The intra-observer study demonstrated a 10% variability in 80% of cases with the 5.5mm probe and 76% of cases with the 8mm probe. The 10% level was a level determined by our medical physics colleagues.

Following the multiple site study, it was decided in order to standardise the method using only readings obtained from the cervix at the 12 o clock position. Readings from the posterior lateral areas of the cervical os were subject to unacceptable variability.

Statistically significant correlations were demonstrated correlating extracellular resistivity with intracellular resistivity, gestation and parity.

The comparison of the non-pregnant and pregnant cervix demonstrated a statistically significant difference ($p<0.001$) in the resistivity readings.

The induction of labour studies demonstrated a statistically significant difference between the unfavourable and favourable cervix ($p<0.034$), but only with the 8mm probe.

No statistically significant results were seen in the post-partum study.

The patient acceptability revealed that the test was almost universally acceptable.

Discussion

This is the first time that electrical impedance studies have been performed on the pregnant cervix. We have shown acceptable inter and intra observer variability. We have demonstrated changes in resistivity measurement associated with parity and gestational age. Clear differences in resistivity readings have been shown comparing the non-pregnant and pregnant cervix and the unfavourable and favourable cervix at induction of labour. These findings have been shown in the context of a new modality of investigation which is highly acceptable to patients.

All our findings conceptually agree with the literature on the pregnant cervix.

These studies are limited by the lack of longitudinal data and in some cases small databases. We feel that this preliminary work shows promise and this investigative modality deserves further investigation.

PAPERS, PRESENTATIONS, PRIZES AND AWARDS EMANATING FROM THIS THESIS

Papers and abstracts

O'Connell MP, Brown BH, Avis NJ, Killick SR, Lindow SW. Electrical impedance - an objective measure of cervical change at induction of labour. *Am J Obstet Gynecol 2001;* **185(6) Suppl:** S206

O'Connell MP, Tidy J, Wisher S, Avis NJ, Brown BH, Killick SR, Lindow SW. Electrical Impedance studies of the pregnant cervix. *Br J Obstet Gynaecol 2000;* **107:**814.

O'Connell MP, Tidy J, Wisher SJ, Avis NJ, Brown BH, Lindow SW. An in-vivo comparative study of pregnant and non-pregnant cervix using electrical impedance measurements. *Br J Obstet Gynaecol 2000;* **107:** 1040-1041.

O'Connell MP, Wisher SJ, Avis NJ, Brown BH, Killick SR, Lindow SW. Tetrapolar measurement of the pregnant cervix using electrical impedance (EI) spectroscopy. *J Obstet Gynaecol 2000;* **20(Suppl 1):** Abst. 95.

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Oral presentations

O'Connell MP, J Tidy,Wisher S, Avis NJ, Brown BH, Killick SR, Lindow SW. Electrical impedance - a new measure of cervical change in pregnancy?. 29th British Congress of Obstetrics and Gynaecology, Birmingham, UK,10-13/07/01.

O'Connell MP, Wisher S, Avis NJ, Brown BH, Killick SR, Lindow SW. An objective measure of cervical ripeness at induction of labour using electrical impedance measurements. XVI FIGO World Congress, Washington, 3-8/09/00.

O'Connell MP. Electrical impedance studies of the pregnant cervix.Blair Bell research Competition meeting, Royal College of Obstetricians and Gynaecologists, London, 15-16/12/99.

O'Connell MP. Tetrapolar measurements of the Pregnant Cervix using Electrical Impedance -The Evidence. East Coast Meeting Hull Maternity Hospital 26/11/99.

O'Connell MP, Wisher SJ, Avis NJ, Brown BH, Killick SR, Lindow SW. Tetrapolar measurement of the pregnant cervix using electrical impedance (EI) spectroscopy. Junior Obstetrics and Gynaecology Society, Royal College of Physicians Ireland, Dublin, 19/11/99.

Poster presentations

O'Connell MP, Brown BH, Avis NJ,Killick SR, Lindow SW. Electrical impedance - an objective measure of cervical change at induction of labour. Society for Maternal - Fetal Medicine, New Orleans, 14-19/01/02.

O'Connell MP, Tidy J, Wisher S, Avis NJ, Brown BH, Killick SR, Lindow SW. Electrical impedance - a new measure of cervical change in pregnancy. 16th European Congress of Obstetrics and Gynaecology (EAGO/EBCOG), Malmo, Sweden, 6-9/06/01.

O'Connell MP, Wisher SJ, Avis NJ, Brown BH, Killick SR, Lindow SW. Tetrapolar measurement of the pregnant cervix using electrical impedance (EI) spectroscopy. British Maternal and Fetal Medicine Society, Royal College of Surgeons, London, 30-31/03/00.

O'Connell MP, Tidy J, Wisher S, Avis NJ, Brown BH, Lindow SW. An in-vivo comparative study of pregnant and non-pregnant cervix using electrical impedance measurements. British Maternal and Fetal Medicine Society, Royal College of Surgeons, London, 30-31/03/00.

O'Connell MP, Tidy J, Wisher S, Avis NJ, Brown BH, Lindow SW. An in-vivo comparative study of pregnant and non-pregnant cervix using electrical impedance measurements. Junior Obstetrics and Gynaecology Society, Royal College of Physicians Ireland, Dublin, 19/11/99.

O'Connell MP, Brown BH, Avis N, Lindow SW. Tetrapolar measurement of the pregnant cervix using impedance spectroscopy. 4th Scientific Meeting RCOG CapeTown, South Africa, 3-6/10/99.

O'Connell MP, Tidy J, Wisher S, Avis NJ, Brown BH, Lindow SW. An in-vivo comparative study of pregnant and non-pregnant cervix using electrical impedance measurements. British Association of Perinatal Medicine, Autumn Scientific Meeting, Imperial College London, 17/09/99.

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European Association of Gynaecologists and Obstetricians Travel Bursary: To partially fund travel to the EAGO/EBCOG meeting in Malmo, Sweden, 6-9/6/01.

Solvey Pharmaceuctical Prize (Overall first prize): 16th European Congress of Obstetrics and Gyneacology (EAGO/EBCOG). .Malmo, Sweden, 6-9/6/01.

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Departmental Nominated Representative: Blair Bell research competition meeting, RCOG, London, 15-16/12/99

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CHAPTER 1 LITERATURE REVIEW

1.1 THE CERVIX - NORMAL STRUCTURE AND FUNCTION

1.1.1 Introduction

The role of the cervix in pregnancy is enigmatic. The characteristics of the cervix permit it to carry out its vital but conflicting functions of acting as a mechanical barrier to retain the conceptus during pregnancy, ripening prior to labour and to allow the uterine contractions to effect dilatation at an appropriate time for the conceptus to be expelled. These physiological changes are all the more remarkable as they the are reversible and can be repeated in any future pregnancy.

This review correlates cervical structure and function with its role in pregnancy and postulates the measurement of these changes using electrical impedance (EI) measurements.

1.1.2 Anatomy

The cervix develops from the uterine body beginning at the 10^{th} week of intrauterine life. By the 20^{th} week it is a clearly recognisable structure (Langman 1974). After birth the cervix constitutes two thirds of the length of the uterus. Two years prior to menarche the uterus hypertrophies, doubling in length and increases tenfold in weight. The majority of this change occurs in the corpus (body of the uterus). It takes approximately 2-3 years to achieve the adult stage of development. In the nulligravida the cervix is tubular and measures 2.5-3 cm in length and approximately the same in external diameter.

The cervix has two openings, the internal os which communicates with the uterine cavity and the external os which communicates with the vagina. The cervical canal is lined with ciliated columnar epithelium and the outer portion lined with stratified squamous epithelium. The squamocolumnar junction is the area that undergoes squamous metaplasia and is the site on the cervix that is at risk of dysplasia and cancer. Hence this is the area targeted when a patient has a cervical smear.

The basic structure of the human cervix is predominantly connective tissue (Danforth 1947) but also contains muscle (Hughesdon 1952).

1.1.3 Connective Tissue

The extracellular matrix in connective tissue consists of the fibrillar component (collagen, elastin, proteoglycans and other proteins) and the non-fibrillar component which is often termed ground substance. The physiological role of each component apart from collagen is poorly characterised.

1.1.3a Collagen

This determines the tensile strength of fibrous connective tissue. The extracellular matrix is made up predominately of Type I collagen with Type III collagen accounting for 20-38% of total collagen content (Kleissl et al 1978). There is also a small amount of Type IV collagen delineating individual smooth muscle fibres and basement membranes of blood vessels (Minamoto et al 1987). Elastin has also been demonstrated in the cervix (Leppert et al 1982). Its role has variously been ascribed to maintaining a closed undilated cervix

throughout gestation and with decreased levels in cervical incompetence (Leppert et al 1987), dilatation of the cervix during labour (Leppert et al 1982) and cervical remodelling post partum (Leppert et al 1986).

1.1.3b Ground substance

The collagen is embedded in the ground substance which consists of glycosaminoglycans (GAGS) which are large molecular weight proteoglycan complexes. They consist of long chains of negatively charged repeating disaccharides, containing one hexosamine and one uronic acid residue. In the non-pregnant cervix the most abundant GAGS are chondroitin and its epimer dermatan sulphate (von Maillot et al 1979, Uldbjerg et al 1983). The binding of GAGS to collagen increases with increasing chain length and charge density.

1.1.4 Cellular Component

The major cellular component of cervical connective tissue is the fibroblast. Cervical fibroblasts are characterised by long dendrites (Uldbjerg 1981). Factors secreted by the cells through the dendrites have a relatively short diffusion distance to any point in the tissue thus allowing fast remodulation of the organ. These cells appear to be responsible for the synthesis of both collagen and ground substance.

1.1.5 Smooth Muscle

While the human cervix is fundamentally a fibrous tissue structure it contains varying amounts of smooth muscle. The lower part of the cervix is the least

muscular with the muscular content increasing from lower to upper cervix and from upper cervix to uterine body. The cervix contains ordinarily 10-15% muscle but occasionally as much as 40-45% (Danforth 1947, Danforth 1954, Rorie and Newton 1967).

The connective tissue component in the cervix is undoubtedly more important than the muscle component. However the muscle component may play a role in the protection of blood vessels during labour and the closure of the cervix post delivery (Calder 1994).

1.2 THE CERVIX DURING PREGNANCY

1.2.1 Changes in the physical properties

The primary function of the cervix prior to labour is to retain the conceptus. At the time of labour it must dilate to allow for the passage of the fetus into the birth canal and within a short period of time post delivery remodel to its pre-pregnancy state in preparation for a future pregnancy. Such a degree of change in such a short period of time is unparalleled in any other organ in the body. Dilatation of the cervix in the non-pregnant and even prior to near the end of pregnancy is often impossible. Hence the use of cervical ripening agents prior to termination of pregnancy to avoid damage of the cervix during mechanical dilatation (Gupta and Johnson 1990).

A clinical scoring system for multiparous patients has been devised as an index of the proximity of spontaneous labour (Bishop 1964). This scoring system

includes cervical position, consistency, dilatation, effacement and the station of the head.

It is felt clinically that the assessment of cervical consistency may be the most important index to occur as it may act as a prelude to effacement of the cervix (shortening of the length of the cervix) and dilatation. Clinically a firm cervix is similar in consistency to the tip of ones nose with a soft cervix being more akin to the consistency of an ear lobe.

1.2.2 Changes in the connective tissue structure

During pregnancy the cervix becomes metabolically more active. There is an increase in the water content from 80.8% to 85.9% (Uldbjerg et al 1983). However after the application of prostaglandin gel the water content remains unchanged (Uldbjerg et al 1981). The water interacts with matrix proteins and destabilises the collagen fibrils and so promotes cervical ripening. The smooth muscle cells become enlarged and may play a role in cervical remodelling post delivery (Calder 1994).

1.2.2a Collagen

The collagen fibres become less densely packed and the waves are broader and deeper during pregnancy. These changes are more marked just prior to and immediately after delivery (Minamoto et al 1987). The collagen content decreases relatively as the water and non-collagen proteins increase in a relatively greater amount. The collagen fibrils are reduced in size at the conclusion of labour (Danforth et al 1960). Biochemically the collagen

concentration also decreases both at term and immediately after delivery when compared with the non-pregnant cervix (Danforth et al 1974, Uldbjerg et al 1983a, Granstrom et al 1989). The close correlation between the biochemical composition of the cervix and the clinical course of delivery in terms of cervical dilatation has been demonstrated. This study randomly selected 27 nulliparous patients and divided them into three groups. Group A included 10 patients with a favourable cervix who laboured spontaneously, group B included 12 patients with an unfavourable cervix and not in labour at term, and group C included 5 patients at the beginning of labour with an unfavourable cervix. Group B patients were treated with 0.5 mg prostaglandin gel. The study demonstrated a significantly longer cervical dilatation time in group C compared with the other 2 groups. This corrrelated with a significantly higher total cervical collagen in group C and demonstrates a potential regulatory role for cervical collagen in cervical function in late pregnancy and early labour (Ekman et al 1986).

1.2.2b Glycosaminoglycans

The total glycosaminoglycan content of the cervix increases two to three fold by term, although the concentration of glycosaminoglycans remains relatively constant. The highest level of glycosaminoglycans is found in cervical tissue obtained just prior to labour. The relative content of hyaluronic acid increases from 5% in the 3rd trimester to 49% in the latent phase of labour (Osmers et al 1993). It is the most prominent glycosaminoglycan in the latent phase of labour and decreases after delivery. Its role may be to loosen the collagenous network

while increasing hyaluronic acid available for binding water, it may also be associated with the increase in tissue hydration and tissue deformity.

1.2.2c Other proteins

The relative amounts of heparan sulphate also increases at parturition and becomes the dominant glycosaminoglycan in the second stage of labour. Chondroitin sulphate in the cervix is relatively low in pregnancy but peaks in the 3rd trimester and decreases in the active phase of labour (Osmers et al 1993).

1.2.2.d Cervical hydration

There is an increase in the water content of the cervix from 80.8% to 85.9% during pregnancy. This was demonstrated on cervical biopsies of 54 women, 15 non pregnant women, 22 nulliparous women in early pregnancy (mean gestational age 11 weeks), 7 women at elective Caesarean section (mean gestation 39 weeks) and 10 women immediately after delivery. The water content was defined as the difference between the wet weight and dry weight of the cervical biopsy. The results show that the water content in early pregnancy was almost identical to that in the non-pregnant group (80.4 +/-0.7% v 80.8+/-0.8%), with an increase in late pregnancy (85.9 +/- 0.5%) and a further slight increase (87.3 +/- 0.5%) in the immediate post natal period (Uldjberg et al 1983). This increase appears to be most dramatic prior to delivery as shown with serial assessment of the hydration index from 34 to 41 weeks on MRI scanning (Oláh 1994). However this study only looked at one patient. The

change in water content corresponds to the changes seen in hyaluronic acid content. Hyaluronic acid has a high water binding capacity (Caplan and Hascall 1980). In comparison to a triple helical collagen molecule of comparable weight, a hyaluronic acid molecule has a much higher volume (Comper and Caurent 1978), which in turn may explain the increased water content of the human cervix at term (Caplan and Hascall 1980). However the increase in water content and its significance is poorly understood.

1.3 THE CERVIX IN PREPARATION FOR LABOUR

1.3.1 Cervical ripening

Cervical ripening is a prelude to the onset of labour and is most obvious in the last 5-6 weeks of gestation. However the mechanism of ripening or maturation remains enigmatic. Clinically ripening refers to the increased softening, distensibility, shortening of cervical length (effacement) and early dilatation which are detectable clinically (Bishop 1964). The changes reflect alteration in the biomechanical properties of cervical tissue and include a reduction in collagen concentration, an increase in water content and a change in glycosaminoglycan composition (Calder and Greer 1992).

The process of cervical ripening has been likened to an inflammatory reaction, with neutrophil invasion of the cervix in labour (Junquiera et al 1980). The interleukins are chemotactic for neutrophils and may represent the commencement of cervical ripening. Interleukin-8 may be involved in neutrophil mediated cervical ripening. In vitro studies have demonstrated the cervix to be capable of producing interleukin-8 in large quantities and that this

production may be influenced by steroid hormones (Barclay et al 1993). Levels of interleukin-6 are elevated in labouring women regardless of gestation (Dudley et al 1994). Elevated levels can thus be regarded as indicative of active labour.

Previously the cervix was regarded as passive once myometrial activity commenced and that cervical dilatation was directly dependent on myometrial activity. The physical state of the cervix has more recently been shown to determine the rate of cervical dilatation and also modulates uterine wall tension and intrauterine pressure (Oláh et al 1991). Those who present with an active myometrium and a non-compliant cervix will generate large intrauterine pressures with relatively mild uterine activity but unless the cervix becomes compliant delivery is unlikely to ensue. At the other extreme is the group who present with a compliant cervix. In this group mild myometrial activity will cause cervical dilatation and so delivery is very likely to occur (Oláh and Gee 1992). The cervix may contract in response to oxytocics during the latent phase of labour (Oláh et al 1993). The presence of such contractions appears to be a feature of the non-dilated and uneffaced cervix. Cervical contractions if observed are only seen during the first 3-4 cm dilatation. These contractions are thought to be caused by the sparse muscle content of the cervix. The net result of these contractions is a redistribution of cervical tissue which may contribute to the process of effacement (Oláh et al 1991). Thus effacement would occur beginning at the external os and leave the internal os the last of the tissue to be affected.

1.3.2 The control of cervical ripening

The factors controlling cervical ripening are incompletely understood.

1.3.2a Prostaglandins

Prostaglandins undoubtedly play a role in the control of cervical ripening in the human. The main prostaglandins produced by the cervix are Prostaglandin E_2 (PGE_2), Prostaglandin I_2 (PGI_2) and Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The ability of the human cervix to produce prostaglandins has been demonstrated in *in-vitro* work (Ellwood et al 1980). In this study tissues were obtained from seven patients undergoing hysterectomy during pregnancy. Four of the patients underwent termination of pregnancy and a hysterectomy at between 7 and 12 weeks gestation. The remaining three patients underwent hysterectomy in the third trimester following Caesarean section. Prostanoid production by the tissues was measured using an *in-vitro* tissue superperfusion technique as described by Mitchell et al (1978). In the first trimester group all tissues studied produced prostanoids in measurable amounts. Values lower than the mean levels in the first trimester were recorded in the patient who underwent elective Caesarean section at 37 weeks gestation. The remaining two patients laboured prior to undergoing emergency Caesarean section and demonstrated high levels of both PGE_2 and $PGF_{2\alpha}$. Physiologically PGE_2 is the most important. The role of $PGF_{2\alpha}$ has not yet attained any clinical importance and so is not discussed further. There are two possible mechanisms by which prostaglandins might affect cervical ripening. Firstly the cervical tissue may be softened as a result of changes in the ground substance, thus allowing a loosening of the bonds between individual collagen fibres. Alternatively the prostaglandins may modify

the binding of collagen and the hydration of the tissue by altering the glycosaminoglycans / proteoglycan components resulting in the degeneration and absolute loss of collagen from the tissues under the influence of lytic enzymes.

There is evidence that prostaglandins act by altering ground substance in cervical tissue (Uldbjerg et al 1981). In this study biopsies of the cervix were obtained immediately before and 15 hours after intra-cervical application of 0.5mg PGE_2 gel in 20 nulliparous patients admitted for termination of pregnancy in the late first trimester. The morphological studies demonstrated an increase in ground substance and a separation/reduction in collagen following the application of the prostaglandin. This was also associated with an increase in fibroblasts.

Increasing collagenolytic activity has been reported with advancing gestational age (Uldbjerg et al 1983) with a concomittant increase in leucocyte elastase activity. However methodologically collagenase activity is difficult to assess. Indeed Rath et al (1987) not only showed no change in collagenase activity but found an absence of collagen breakdown fragments on electrophoresis of the tissue extracts taken from pregnant human cervices which were treated with the prostaglandin analogue Sulprostone, compared to placebo treated cervices, suggesting no role for prostaglandin therapy in the direct stimulation of collagenolytic activity *in-vivo*.

PGE_2 mediated cervical ripening may be explained by alterations in glycosaminoglycan content that will disperse and destabilise the collagen fibrils and so increase tissue compliance.

Other possible mediators of cervical ripening include;

1.3.2b Oestrogens

Oestradiol has been used to ripen the unfavourable cervix (Gordon and Calder 1977). In this study 50 primigravida patients were randomised either to receiving 150mg oestradiol in viscous gel or the viscous gel alone at the time of induction of labour. All the participants had a modified Bishop score 0-3. At induction of labour the following morning there was a significantly greater increase in the cervical score in those that received the oestradiol. Indeed after induction of labour the mean interval to delivery was 10.5 (+/- 3.6) hours in the treatment group and 14.3 (+/- 3.9) hours in the control group. The data supports a role for oestradiol in the process of cervical ripening. The mechanism underlying the ripening is putatively by induction of prostaglandin synthesis.

1.3.2c Progesterone and antiprogestins

The role of progesterone in the cervical ripening process in humans is poorly characterised. Progesterone appears to have an inhibitory role on cervical ripening and parturition in animals where a fall in progesterone at term results in ripening and labour. Such a fall does not occur in humans but progesterone's anti-inflammatory role could inhibit the ripening process by inhibiting neutrophil influx and activation. This possibility is supported by the ripening effects of antiprogestins on the cervix prior to termination of pregnancy. Antiprogestins have been shown not only to decrease the force required to dilate

the pregnant cervix but also exhibit a role in cervical dilation prior to termination of pregnancy (Gupta and Johnson 1990).

1.3.2d Relaxin

Relaxin may be involved in cervical ripening but our understanding of its role is unclear. Potentially, unlike prostaglandins, it may effect cervical ripening without having an effect on myometrial contractility. Recombinant human relaxin has been used without success in clinical studies (Bell et al 1993). Overall the specific role of relaxin in human pregnancy is unknown. If relaxin were to prove an effective pharmacological agent for cervical ripening in the clinical setting it would have the advantage of being selective on the cervix, avoiding stimulation of the myometrium.

1.3.2e Inflammatory mediators

Cervical ripening is considered to be a physiological inflammatory process characterised by an accumulation of neutrophils in the cervical stroma (Junqueira et al 1980). Biopsy specimens of cervical tissue of normal patients during pregnancy (n=16) and biopsy specimens from non-pregnant sexually active women (n=10) were studied by electron microscopy. Optical and electron microscopy revealed neutrophilic polymorphonuclear leucocytes in all specimens from the intrapartum cervices but not in the non-pregnant cervices. Interleukin-8 is produced by the cervix and can induce cervical ripening by inducing neutrophil migration and by causing degranulation of the specific granules that contain collagenase (Barclay et al 1993).

1.4 CONCLUSIONS

The cervix must be regarded as a dynamic structure, the control of which is incompletely understood. A greater understanding of the cervix is required in order to characterise its changes in both term and more importantly idiopathic preterm labour. Such knowledge of its function would not only progress our understanding of cervical physiology but also allow for clinical interventions in the management of pregnancy and labour problems. Electrical impedance measurements of the pregnant cervix may offer an non invasive objective measure of cervical change both during pregnancy and labour.

1.5 BIOIMPEDANCE MEASUREMENT

1.5.1 Introduction

The detection of biological signals to measure physiological variables is not new. G.N Stewart (1894) studied circulation times between different body organs using electrical conductivity of blood at the end of the nineteenth century. In his seminal paper he postulated that "since the electrical conductivity of blood is practically that of a solution of the salts in it, it can readily be altered by injection of a solution of common salt of sufficient strength. The alteration will travel on with the velocity of the blood system, and on arrival of the altered blood at any point of the vascular system may be detected by an easy galvanometrical observation, without the necessity of opening the blood vessel."

Indeed in 1899 he detected bacterial growth for the first time by measuring conductivity changes of the culture medium, thus giving birth to current impedance bacteriometry (Stewart 1899).

Between 1924 and 1944 Kenneth S. Cole published fundamental papers concerning biological impedance (Cole 1928a, Cole 1928b, Cole 1932, Cole & Curtis 1939, Cole & Guttman 1942, Cole & Curtis 1944). He studied the impedance offered by suspensions of spherical particles (Cole 1928a) and of arbacia eggs (Cole 1928b) presenting an equivalent circuit and graphical descriptions for the vector impedance and for it's modulus. *Arbacia punctulata* is an equinoderm that lays eggs that are essentially spherical and so yield the electrical resistance of a homogenous suspension of spheres, such that,

$$(r_1/r-1)/(r_1/r-2) = k\,(r_1/r_2-1)/(r_1/r_2-2) \qquad 1.5.1$$

r = resistance of suspension r_1 = resistance of the liquid phase

r_2 = resistance of the spheres k = spheres' volume concentration

resistance's are expressed in Ohms/cm^3.

In Cole's work frequency was used as an independent variable. However in biological impedances, unlike technological circuits, as the centre of the circumference does not lie on the horizontal axis, Cole & Curtis (1944) reviewed this biological feature of phase angle shift - in essence a measure of the leak current of the system. Herman P. Schwan studied the electrical properties of different kinds biological tissues (Schwan 1955, Schwan 1985a,

Schwan 1985b, Schwan & Kay 1957, Schwan & Li 1953) and developed techniques to make measurements at different frequency ranges (Schwan 1963).

1.5.2 Tissue as a leaky dielectric

Tissues contain both free and bound charges and so simultaneously exhibit the properties of a conductor (in that it contains free charge carriers and so can be described in terms of its conductivity) and a dielectric (in that bound charges are also present which can be expected to give rise to displacement currents when an electric field is applied). If tissue is regarded as a conductor then we must include a term in the conductivity to account for the redistribution of bound charges in the dielectric. Conversely if we view tissue as a dielectric then we must include a term in the permittivity to account for the movement of free charges. Hence the electrical properties of tissues over a wide range of frequencies can be described using two properties, namely relative permittivity ε^* and conductivity σ (fig. 1.1).

If the dielectric has relative permittivity ε_r, then the slab has a capacitance

$$C = \varepsilon_0 \varepsilon_r A / x \qquad 1.5.2$$

The conductance of the slab is

$$G = \sigma A / x \qquad 1.5.3$$

These equations define the static capacitance and the conductance of the dielectric.

Applying an alternating voltage to the dielectric, the current will lead the voltage. If $G = 0$, the phase angle $\theta = \pi/2$ and so the current leads the voltage by $\pi/2$, as would be expected for a pure capacitance. If $C = 0$ current and voltage are in phase as expected for a pure resistance, the admittance is given by

$$Y^* = G + j\omega C \qquad 1.5.4$$

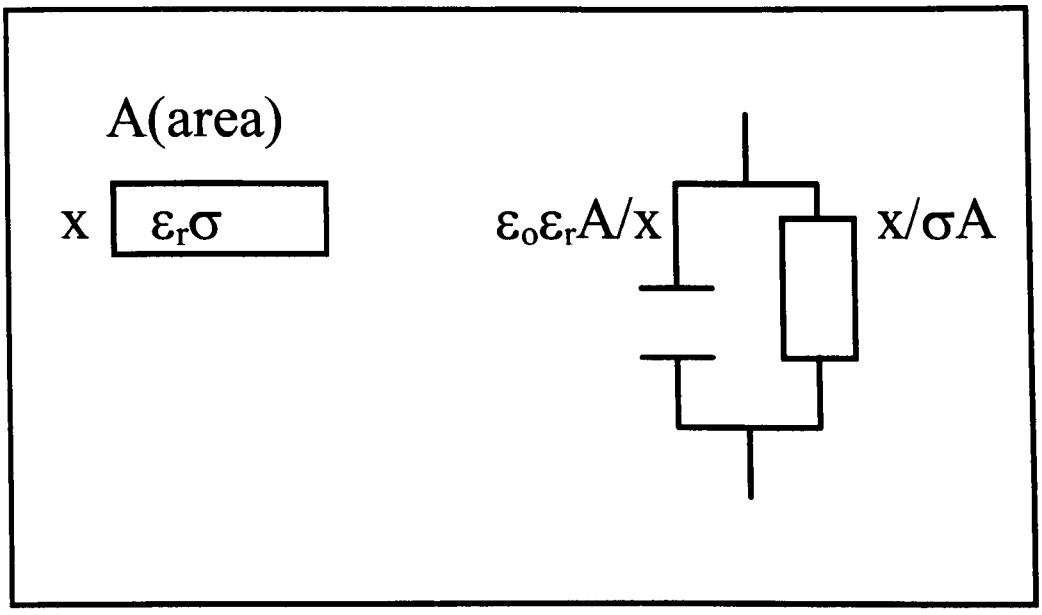

Figure 1.1 Tissue with both capacitive and resistive properties in parallel. Cross-sectional area A, thickness x with a conductivity σ, relative permittivity ε_r and its equivalent electrical circuit.

In general the electrical properties of tissue can be expressed in terms of a generalised permittivity

$$\varepsilon^* = \varepsilon' - j\varepsilon'' \qquad 1.5.5$$

This includes the effect of both the resistive and capacitive elements in the real dielectric. ε' is the real part and ε'' the imaginary part (the dielectric loss which includes both the component of free charge conductivity and the component of bound charge displacement).

We can thus relate the generalised permittivity to the model of the real dielectric by considering the admittance:

$$Y^* = G + j\omega C = A/x\ (\sigma + j\omega\varepsilon_0\varepsilon_r) \qquad 1.5.6$$

It is possible to consider the admittance in terms of a complex conductivity:

$$Y^* = G + j\omega C = A/x\ (\sigma + j\omega\varepsilon_0\varepsilon_r) = A/x\ \sigma^* \qquad 1.5.7$$

It is therefore possible to relate the behaviour of the conductivity and permittivity.

1.5.3.Transducers

A transducer is an element that converts one type of input energy into another type of output energy. For transduction to be possible the biological system must provide at least one transducible property, (e.g. change in hydration of the cervix).

General characteristics required of biomedical transducers include amplitude and phase linearity, good sensitivity, fast-time response, easy calibrability, precision, accuracy and stability.

1.5.4 Impedance

Impedance is a quantitative measurement of the hindrance offered by a given system when an applied force like quantity tries to cause or maintain the passage of a fluid-like quantity through the system.

It is thus conceivable that a physiological variable might produce a change in the electrical impedance offered by a biological system between any two points. An impedance meter could be connected to such points yielding as it's output a signal proportional to the physiological variable (change in cervical hydration) but in terms of impedance either modulus or phase or both. The impedance meter plays the role of a transducer.

Changes in resistivity, permittivity, or the geometry of the system under study will induce modifications in the biological impedance offered by that system which must be allowed for in *in-vivo* studies.

1.5.5 Effects of electric current on biological tissues

Biological tissue contains free charge carriers and so can be described in terms of conductivity. Bound charges are also present in tissue so that dielectric properties also exist and can be expected to give rise to displacement currents when an electric field is applied. Biological tissue also contains mechanisms for the active transport of ions.

Conductivity is the dominant factor when frequencies less than 100 kHz are applied to the tissue. The electrical resisitivity of a range of tissues is shown in table 1.1.

Tissue		Resistivity	Frequency
CSF		0.650Ωm	1kHz - 30kHz
Blood		1.46 -1.76Ωm	1kHz - 100 kHz
Skeletal Muscle	longitudinal	1.25 - 3.45Ωm	100Hz - 1kHz
	transverse	6,75 -18.0Ωm	100Hz - 1kHz
Lung	inspired	17.0Ωm	100kHz
	expired	8.0 Ωm	100kHz
Neural Tissue	grey matter	2.8Ωm	100kHz
	white matter	6.8Ωm	100kHz
Fat		20Ωm	1kHz - 100 kHz
Bone		> 40Ωm	1kHz - 100kHz

Table 1.1 The electrical resistivity of a range of tissues.

1.5.5a Frequency dependence

The impedance of biological tissues varies with frequency and varies from tissue to tissue (Lu et al 1996). The dielectric properties of all tissues tend to follow the same dependence on frequency. For frequencies below 10kHz ionic polarisations lead to very large values for the relative permittivity. These polarisations are greatly reduced as the integrity and physiological viability of the tissue is impaired. For frequencies between 100kHz and 100 MHz there are large changes in the dielectric properties associated with the resistive nature of cell membranes. As the integrity of the cell membrane is lost the dispersion is greatly reduced, so necrotic tissue looks dielectrically different from normal tissue. At frequencies above 100 MHz differences between tissue types are largely lost (Pethig 1987). At all frequencies dielectric properties are directly associated with tissue water content (Pethig 1984). This in essence is the aim of our present work attempting to characterise the pregnant cervix in terms of its dielectric properties associated with the physiological change in cervical hydration with increasing gestation particularly in the pre-labour phase.

1.5.5b Safety considerations

The measurement of biological impedance requires the passage of an electric current through the tissue under study. Obviously no harm or disturbance of any kind should happen to the tissue under study. In physiological terms no excitable tissue should be stimulated.

1.5.5c Stimulation

All excitable cells are sensitive to the passage of an electric current across their membrane, triggering an action potential if the stimulating current is adequate. When the stimulation is not adequate, the response is sub-threshold (Geddes & Baker 1989). The impedance technique operates with an external current which must not elicit any response from the tissue. Thus the biological stimulation criteria should not be met by this detecting technique.

1.5.5d Excitability curves

The electric response of a cell is obtained when a given amount of electric charge crosses the cell membrane. A large current applied during a short period can trigger the same response as that of a smaller current applied over a longer time period. The latter situation finds a limit as there is a value (Rheobase) that has to be applied for an almost undetermined length of time to elicit a response. Currents lower than rheobase will never trigger a response. For given excitable tissue, it will be more difficult for short pulses to elicit a response and if these are repetitively applied, they will correspond to a high frequency that will be ineffective.

1.5.5e Limits in electric shocks

When the electric current applied to an individual is adequate to elicit responses from excitable tissues, in general, sensation, pain, or contractions may occur depending on the tissues involved. In general the threshold of sensation rises with increasing frequency of the applied current.

At very low frequencies (below 0.1Hz) a stinging sensation occurs under the electrode. The major effect is thought to be electrolysis at the electrode tissue interface.

At frequencies above 10Hz the dominant effect is that of neural stimulation. Placing the electrode over a large nerve trunk causes sensation arising from the most rapidly conducting sensory fibres. Increasing the amplitude recruits the more slowly conducting fibres and so motor contractions occur.

Values greater than 15mA.rms depending on the current path will produce respiratory arrest, marked fatigue and intense pain. The region for fibrillation lies between 50 mA.rms and 5-6 A.rms. Still higher values will induce sustained myocardial contraction and/or severe burns.

Therefore electric currents applied for a biological impedancemetric measurement must always lie within the region below the threshold strength/duration curve of the excitable tissues found in the expected current pathway.

The recommendations for the safety and constructional standards for patient connected equipment are contained in an international standard drawn up by the International Electrotechnical Commission (IEC). According to IEC 601 the recommended safe intensity value should be lower than 1 mA.rms. The maximum sensitivity of excitable tissues is found by and large between 20 Hz and 100 Hz. Thus these frequency ranges should not be used.

1.5.6 Elements of the impedancimetric circuit

1.5.6a Technological counter part

If a voltage (E) is applied across any biological tissue a current (I) will tend to traverse the tissue finding an electrical impedance that is mathematically described by the complex relationship between E and I (fig 1.2).

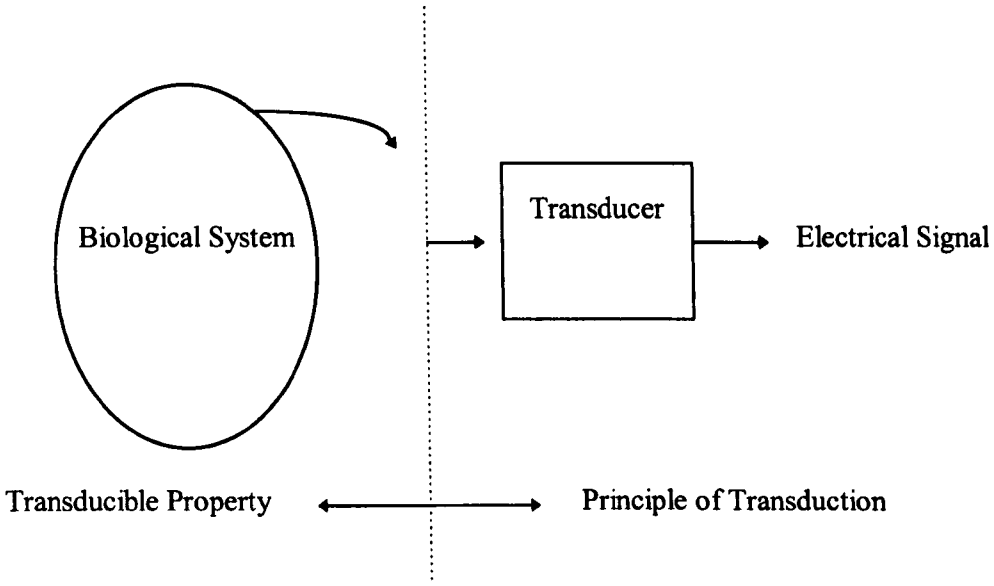

Figure 1.2 The impedancimetric circuit as applied to a biological system.

The impedance (Z_B) usually shows a constant component (Z_O) and a time dependent variational part (ΔZ) which may vary with different factors of the living tissue, such as it's geometry, temperature, biochemistry or others. Thus

$$Z_B = Z_O + \Delta Z \qquad 1.5.8$$

This is a unique impedancimetric characteristic of each biological tissue (Cole 1932, Fricke 1925a, Fricke 1925b). With high frequencies, the electric current traverses easily through the cell membrane while with low frequencies the membrane prevents a high impedance pathway and the current prefers the electrolyte solution. In the case of excitable tissue Cole & Curtis (1939) demonstrate that the membrane impedance changes during the development of the action potential.

1.5.6b Electrolyte/electrode interface

In order to measure and record potentials and hence currents in the body, it is necessary to provide some interface between the body and the electronic measuring apparatus. This interface is carried out by using biopotential electrodes. These electrodes must be able to conduct a current across the interface between the body and the electronic measuring circuit.

Measurements of the impedance of biological tissue involve making an electrode contact with the tissue. This electrode forms a tranducer between the ionic flow in the tissue and the electronic flow in the recording equipment. The transducer will have an impedance which cannot be neglected when making tissue measurements and so it is necessary to consider the electrical equivalent circuits of the electrodes (Barber and Brown 1984). The effect of electrode

impedance is reduced when using a tetraoplar set up as the current is driven through a separate pair to the pair that receives the received voltage.

1.5.6c Basic circuit configuration to measure impedance

The biological impedance offered by the system under study represents the first element from which a signal is obtained to be physiological or clinically interpreted. To detect this the electrodes are placed so that an interface is always introduced. Over it's impedance we have only a relative control. The third portion of the total impedancimetric circuit is the electronic section. Most of the measurements yield only the modulus and how much biological information may be contained in the phase angle is not known.

In biology or physiology the most common and simplest method to measure impedance modulus is through the measurement of voltage and current. There are two basic configurations, bipolar and tetrapolar. The tetrapolar configuration is described, as this is the configuration employed in the work presented.

1.5.6d Tetrapolar constant control

With this configuration the current enters into the tissue via two injecting electrodes (current electrodes) while the signal is picked up by a second pair of electrodes (voltage electrodes).

The injected current is independent of the electrode/electrolyte interface impedance and of the biological impedance. This condition is best satisfied when the current source impedance is large compared to the sum of the interface and tissue impedances. If the current electrodes are a distance from the voltage

electrodes the two latter would detect a signal in a region with more uniform distribution of current lines thus favouring an output/input linear relationship. Anatomical or size limitation may impose practical restrictions on these desirable conditions. The circuit is almost immune to movement artifacts or to changes in the interface impedance compared to the bipolar arrangements.

1.5.6e Phase measurement

To date this has not been exploited in biology and physiology. Whatever method is used the frequency and amplitude selection must be kept within the electric safety criteria recommended in clinical engineering.

1.5.7 Impedance spectrometry

1.5.7a Introduction

The first contributors in this area date back to the end of the nineteenth century. In 1912 Hober demonstrated on blood that the membrane limited the passage of low frequency current through the cell, but allowed the high frequency current to pass through thus manifesting a capacitance aspect of the cell membrane, demonstrating that tissue was a conductor and its resistance varied with frequency.

In 1921 Crile et al proposed comparisons between the electrical conductivity of healthy and pathological tissue. McLendon, (1926) was the first to measure both components of the complex impedance of biological tissues. Fricke & Morse, (1926) demonstrated that the capacitance of breast carcinoma was higher than that of healthy breast tissue.

The characterisation of normal and pathological tissues based on the knowledge of their electrical properties using electrical impedance spectrometry forms the basis of our current studies.

1.5.7b Dielectric materials

The electrical properties of tissue are a direct consequence of the composition and structure of the tissues. In biological tissues, electric current influences those component parts that have an electric charge. One can adapt the relationships established by Maxwell (1881), Debye (1929), Fricke (1932), to look at the analogy existing between the phenomena occurring in a dielectric and in biological tissues at the microscopic level . However, complex electrical impedance is better defined on the macroscopic scale.

Dielectric materials, although usually associated with substances capable of storing electrostatic energy, can also be applied to substances capable of depolarization under the effects of an electric current. The polarisation of a medium results from molecular deformation and molecular orientation.

At low frequency, since the polarization and the electric field are in phase no dielectric loss is observed. However as the frequency increases there ensues a decrease in permittivity due to dielectric losses and an associated increase in conductivity.

In considering dielectric relaxations two equations are worth discussing;

(1) Debye equation

(2) Cole equation

When a capacitor is charged, the applied electric field E either creates or orientates electrical dipoles within the material. This process is called polarisation. By making the assumption that the process of polarisation has an exponential approach to its final value it can be shown that the real and imaginary parts of the complex permittivity will be given by:

$$\varepsilon^* = \varepsilon_\infty + (\varepsilon_s - \varepsilon_\infty) / 1 + j\omega\tau \qquad 1.5.9$$

ε^* = Complex permittivity ε_∞= Permittivity at very high frequency

j= Ortogonal direction ε_s= Permittivity at very low frequency

ω= Angular frequency τ= Relaxation time

Dipolar relaxation in the Debye sense (Debye 1929) is an effect of a purely viscous process without any restoring force - therefore the first order.

It does not take into account the influence of static conductivity whose contribution to the complex permittivity cannot be ignored. When measurements of the relative permittivity are made over a wide range of frequencies, it is found that the results do not agree with the prediction of the Debye model. Therefore the Debye equations do not make it possible to model heterogeneous media well e.g. biological tissues, since the dielectric relaxation of most of the biological substances is more complex and involves several time constants.

The relaxation function most widely used is that proposed by Cole (1940). This is based on a distribution of relaxation time constants, thus making it possible to experimentally observe the dielectric behaviour of the observed tissues. The complex permittivity is given by the Cole equation (1940) often termed the 'Cole - Cole' equation (Cole & Cole 1941). This formula is similar to the Debeye equations but has an additional term called alpha (α).

$$\varepsilon^* - \varepsilon_\infty = (\varepsilon_s - \varepsilon_\infty) / [1 + (j\omega\tau)^{(1-\alpha)}] \qquad 1.2.7$$

ε^* = Complex permittivity ε_∞= Permittivity at very high frequency

j= Ortogonal direction ε_s= Permittivity at very low frequency

ω= Angular frequency τ= Relaxation time

α= Constant for the tissue under study

Alpha can be choosen to give a good fit to the measured data. It is clear that if $\alpha = 0$, the equation reduces to the Debye model. This improved the agreement between the theoretical and measured values. The Cole - Cole model is a model of measured data. It has been applied to a wide variety of materials and interactions over the past 60 years, but it gives no information about the underlying causes of the phenomena being measured.

1.5.7c Biological media

Jossinet (1995) described the fluid mosaic model of cell membranes. In this model when an electric field is applied, the charged ions move and accumulate on both sides of the membrane. If the field is alternating it is conceivable that above a certain frequency the charges no longer have time to accumulate. A polarisation-relaxation then occurs for frequencies of the order of kilohertz. At

lower frequencies polarisation-relaxation of organelles and cells occurs. At high frequencies, the polarization-relaxation of small molecules such as water predominates.

The electrical behaviour of biological tissues reveals a high frequency dependence of the electrical parameters due to various relaxation phenomena that occur when a current passes through the tissue. As the frequency of the applied electric field increases, the conductivity of most tissues rises. This increase in conductivity is associated with a decrease in permittivity. This decrease occurs in three main steps (Schwan 1957).

The first is alpha dispersion, which predominates at low frequency (10 Hertz to a few kilohertz) characterised by a very large permittivity variation arising from interfacial polarisations associated with electrical double layers and surface ionic conduction effects occurring at membrane boundaries. It is associated with numerous cell membrane-electrolyte interfaces in the tissue, thus it is a surface phenomenon.

The second is beta dispersion which occurs in the radiofrequency range (tens of kilohertz to tens of megahertz). It is essentially due to the capacitive charging mechanism of cell membranes, its origin lying in the basic structure of the cell in which the membrane separates two conducting media. When the frequency increases the cell capacitive reactance decreases which induces an increase in the current flow passing through the intracellular medium and so an increase in tissue conductivity.

The third is gamma dispersion which dominates in the high frequency spectrum. This dispersion is due mainly to reorientation of the electric dipoles formed by the tissue water molecules.

Figure 1.3 shows a schematic diagram of the three major dispersions.

In summary, at low frequencies the measurement of complex impedance provides information at the extracellular and membrane level and the information acquired relative to the cell structures concerns increasingly internal parts of the cell as the frequency increases.

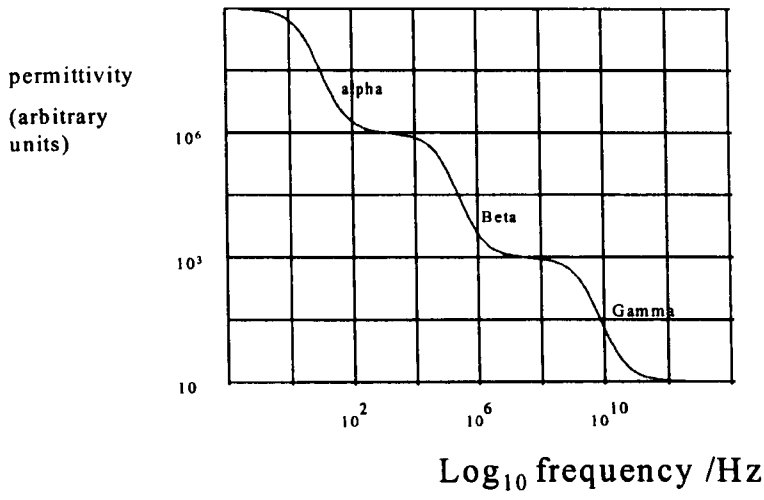

Figure 1.3 Schematic representation of the three major dispersions in biological tissue. Permittivity is shown as a function of frequency.

1.5.7d Method of measurement and modelling

Electrical impedance is measured by passing a small current through tissue via electrodes on the tissue surface and measuring the resulting potential differences around the boundary of the body surface. The conductivities of the various tissues can be calculated.

When an electric current passes through tissue it will pass either through the extracellular space or through both the intracellular and extracellular spaces. This can be modelled simply by two parallel branches, one through the extracellular space and the other through the intracellular space. The branch through the extracellular pathway is thought to be purely resistive. The branch through the intracellular pathway incorporates the capacitive effect of the cell membrane. The magnitude of the measured impedance will be frequency dependent. This complex model can be represented by an electrical circuit where the intra- and extra- cellular resistances are represented by S and R respectively. The cell membrane the separates the two is represented by a capacitor C (figure 1.4).

It has been shown that if measurements are made over a range of frequencies and analysed in terms of Cole Plots, then the contributions from the intracellular and the extracellular sp-aces can be separated (Rigaud et al 1994). According to the RSC circuit used to represent a cell, at low frequencies, since the impedance of the cell membrane is very large, current flows mainly in the extracellular space. Therefore information about the extracellular fluid can be obtained from measurements made at low frequencies. At high frequencies current flows

through both the intracellular and extracellular spaces and so information about the intracellular fluid can be obtained from measurements at both low and high frequencies.

This is the modelling that has been applied to the work presented in this thesis.

1.5.8 Summary

In this review of the literature, the historical background of impedance measurements has been outlined. Biological tissues have been characterised as a leaky dielectric acting as conductors and insulators simultaneously. The safety factors involved in impedance measurements has been highlighted, as has the effect of electric currents on biological tissues. The elements of an impedancimetric circuit have been described with particular emphasis on the tetrapolar probe. Impedance spectrometry has been introduced highlighting the relaxation factors involved in measuring biological tissues. Particular emphasis has been laid on the Cole-Cole equation and the method of modelling using this equation.

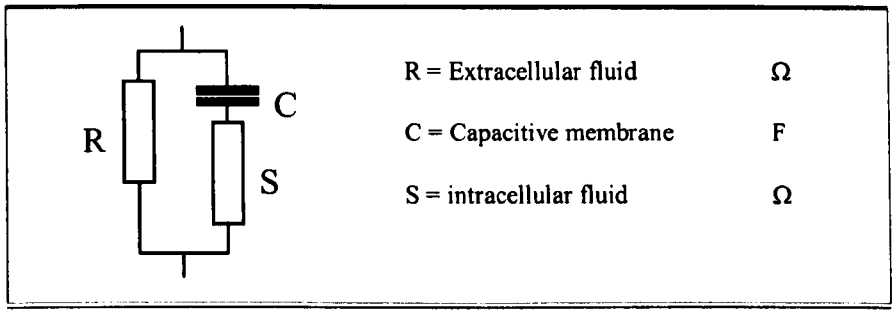

Figure 1.4 A simple electrical circuit repesenting a biological cell.

1.6 ELECTRICAL IMPEDANCE MEASUREMENTS IN OBSTETRICS AND GYNAECOLOGY

1.6.1 Introduction

Electrical impedance measurements have been utilised in detecting physiological and pathological change in a variety of situations in obstetrics and gynaecology. Early work concentrated on the prediction of pelvic venous congestion using electrical impedance tomography (EIT) imaging. More recently bioelectrical impedance has been used to assess female fertility. In obstetrics impedance measurements have been used to assess fetal lung maturity. However with the development of the tetrapolar probe the *in-vitro* work on the cervix can now be performed *in-vivo.* Gynaecological uses centre on the prediction of cervical intra-epithelial neoplasia and cervical cancer. Obstetrically the tetrapolar probe is being used to assess the cervix in pregnancy. This is the subject of this thesis.

1.6.2 Pelvic venous congestion

Electrical impedance imaging or applied potential tomography is a non-invasive method of producing images of the way in which the body tissues conduct electricity (Seagar et al 1987, Brown et al 1988). As blood has an electrical conductivity twice that of muscle, ten times that of fat and one hundred times that of bone it follows that a rise in tissue conductivity is mainly due to an increase in blood content. It was this fact that was utilised in an attempt to

characterise the changes in pelvic venous circulation in response to a change in posture in women with pelvic congestion (Thomas et al 1991). Twenty seven women participated in the pilot study. Fifteen had normal pelvic vasculature on ultrasound scanning, and twelve had congestion diagnosed by venography (Beard et al 1984). The results demonstrated a significant increase in blood volume, in both those with pelvic congestion and the controls, with a change in posture from supine to the standing position. However there was no significant difference between the groups. The blood volume changes were confined to the anterior / central areas in the control group, whereas in those with pelvic congestion there was a greater involvement in the posterior part of the pelvis. Using a ratio of posterior to anterior blood volume changes (cut - off point 0.4) it was possible to distinguish those with pelvic congestion from a normal group with a specificity of 87% and a sensitivity of 75%. This non invasive test compared well with venography (specificity 91%, sensitivity 89%). While the resistivity changes were attributed to blood volume changes in the pelvis, these changes were not quantifiable. *In vitro* work using a cylindrical tank 40cm high, threaded externally at one end, made from Perspex tubing with an outside diameter of 18cm, with a wall thickness of 5mm has since allowed for the possible quantification of blood volume changes in the human pelvis (Thomas et al 1993). In this experiment sixteen equidistant holes were drilled around the circumference of the tank to accept brass electrodes, and a single hole was drilled near the base of the cylinder to accept a common electrode. Tubing manufactured from a semi-permeable membrane was used to simulate pelvic veins. Two saline solutions were used in the experiment, the tank being filled

with a solution having a resistivity of 5Ωm (the average resistivity of the human thorax) and the tubing being filled with a solution with a resistivity of 1.5Ωm which is similar to blood. EIT images were processed to generate three values per image; the maximum value of resistivity change (peak), the number of pixels associated with that peak whose value was greater than 50% of the maximum (area) and an integral of the pixel value over that area (integral). The resistivity integral was found to have the best correlation with volume change. However the relationship was non-linear and so if this technique were to have a clinical value,correction algorithms would have to be developed.

To date EIT is not employed in the clinical setting in the assessment of pelvic venous congestion.

1.6.3 Assessment of female infertility

Chronological age, serum concentration of follicle stimulating hormone (FSH) in the early follicular phase of the menstrual cycle (basal FSH) and the clomiphene citrate challenge test are widely used to estimate female fertility but correlate only with large declines (Scott and Hofmann 1995). Changes in bioelectrical impedance may reflect female fertility better than these conventional parameters (Jinno et al 2000). In this study bioelectrical impedance was measured daily between the right and left arms in a sitting position by the tetrapolar method. Two detector electrodes were placed in the middle of the dorsal surfaces of the right and left wrists and an excitation current of 800μA, A.C. at 50kHz was introduced at two current -injector electrodes placed 3cm distally beyond the detector electrodes.

Using the conventional criteria namely basal FSH, body height, and body mass index, on day 4 of the luteal phase prior to the *in-vitro* fertilisation (IVF) cycle no significant difference was evident between those who subsequently conceived against those who failed to conceive. The mean age was lower and the bioelectrical impedance was significantly increased in those who conceived following the IVF cycle. Stepwise multiple logistic regression analysis showed that of the five factors the bioelectrical impedance alone was a predictor of pregnancy and that for each Ohm (Ω) increase, the likelihood of successful conception increased by 1.0059 fold.

Classifying the bioelectrical impedance into <600Ω and ≥ 600Ω, the rate of pregnancy per cycle was significantly higher in those with a bioelectrical impedance of ≥ 600Ω on day 4 of the luteal phase prior to the IVF cycle.

Bioelectrical impedance probably reflects female fertility by indirectly measuring the angiogenic capacity of the reproductive organs. It is known that angiogenesis is a fundamental requirement for normal development and function of follicles, corpus luteum, and endometrium (Reynolds et al 1992) in which vascular endothelial growth factor (VEGF) plays a role by increasing vascular permeability and inducing endothelial cell proliferation (Ferrara and Davis-Smyth 1997). The fluid shifts induced by VEGF are likely to synergistically reduce fluid in the upper body including the arms. Consequently the bioelectrical impedance between the wrists increases in the luteal phase.

Abnormal values in FSH and the clomiphene citrate challenge test appear to be a late finding in diminished fertility, which is consistent with basal FSH having a high specificity but extremely low sensitivity for predicting failure in IVF

cycles. When bioelectrical impedance measurements suggest good fertility, the pregnancy rates are high regardless of age, while prediction of poor fertility by bioelectrical impedance still does not effect an age related decline in pregnancy rate. Thus it may be that decreased bioelectrical impedance is an early finding in decreasing fertility.

This study highlights the a potential role for bioelectrical impedance measurements as a screening tool for subfertility, by offering a sensitive, non-invasive, rapid, and inexpensive test that facilitates conception prior to infertility becoming overt and ultimately declining.

1.6.4 Screening test for cervical precancerous change

In this study of 124 women (Brown et al 2000), impedance measurements were made with a pencil probe of 5.5mm in diameter, with four gold electrodes placed flush with the face of the probe. A current of 10μA peak to peak was passed between an adjacent pair of electrodes and the real part of the resulting potential was measured between the remaining two electrodes. The measurements were made at eight frequencies by doubling the frequency in steps between 4.8 kHz and 614 kHz. The probe was calibrated in saline of known electrical conductivity. The measurements were made in the colposcopy clinic. The impedance data was correlated with the colposcopic and histological data. The impedance data was fitted by a least square deviation method (Brown et al 1995) to a Cole equation (Cole and Cole 1941).

The results were expressed in terms of R which is related to the extracellular space (impedance at very low frequency) and S which is related to the

intracellular space (impedance at very high frequency). The values for R and S separated normal squamous epithelium tissue from the cervical intra-epithelial neoplasia 2/3 (CIN) tissues ($p< 0.0001$ for each variable). R and S also separated normal squamous epithelial tissue from CIN 1 tissue ($p< 0.0001$ for each variable). S separated CIN1 from CIN 2/3 tissues ($p=0.0009$). A Pearson correlation was performed to assess the statistical independence of the estimated values for R and S. An $r^2=0.086$ indicated that only 8.6% of the variation in R could be attributed to S and vice versa.

To assess the usefulness of the technique for screening receiver-operating-characteristic curves (ROC) were constructed. The R/S minimum were compared with the CIN/normal classification by the ROC means. The area under the curve was 0.819. Patients were categorised on the basis of the impedance results and the 0.81 value for R/S minimum was described as borderline. Using these criteria the impedance measurements yielded a sensitivity of 75%, a specificity of 71% , a positive predictive value of 89% and a negative predictive value of 45%. In the study cervical cytology had a positive predictive value of 76%.

The observed changes seen in the R and S values in this study fit well with the changes expected in both the physiological and pathological situations under study. The technique showed potential in its secondary objective of assessing the technique as a screening tool for precancerous change in the uterine cervix.

1.6.5 Assessment of fetal lung maturity

The aim of this study was to develop a new technique to measure phospholipid concentration in amniotic fluid that would be less invasive than currently used modalities, namely amniocentesis and nuclear magnetic resonance spectroscopy, while allowing good reproducibility and accuracy (De Luca et al 1996).

The underlying theory was that as phospholipid concentrations changed in pregnancy, particularly in the third trimester, the electrical conductivity would mirror this change. The authors assumed that amniotic fluid could be considered as a homogenous medium akin to a physiological saline solution. This is a potential source of error in the study as the authors ascribed all the change in conductivity to changes in components and concentrations of the various phospholipids and did not allow for changes in osmolality, sodium, creatinine, urea and cytological changes seen with increasing gestation (Lind 1969).

The measurements were carried out using two Hewlett-Packard impedance analysers one in the frequency range 10kHz to 10MHz and the other in the frequency range 0.5MHz to 100MHz. Measurements were performed at a temperature of 20°C (within 0.1°C) immediately after the samples were collected. However in some cases samples were analysed after being stored for a number of days at 5°C. In these cases the conductivity values were within 0.5% of the initial value.

In total 85 amniotic fluid samples were analysed at different stages of pregnancy. Of concern with the results section is that the electrical conductivity measurements are superimposed on a graph of Gluck's (1971) original work on

phospholipid concentrations. No attempt was made to measure the phospholipid concentrations in the specimans analysed.

The study did allow for the possible influence or interference of different substances that could accidently contaminate the amniotic fluid during amniocentesis, namely blood and meconium. No difference was observed.

The study demonstrated a significant fall in electrical conductivity with increasing gestation. This decline was most notable at later gestations. In the conclusion the authors postulated the development of an *in- vivo* model to measure the electrical conductivity of amniotic fluid.

1.6.6 Modelling of the cervix in late pregnancy

Avis et al (1996) reported the results of a pilot study to measure the *in-vitro* electrical impedance of samples of cervix taken at Caesarean section from six patients at various stages within the third trimester of pregnancy.

In the study a sample of the cervix was excised from the upper segment of the cervix at Caesarean section after delivery of the baby. Eleven patients were initially recruited but data was only obtained from six. No explanation is given for this in the paper. Of the six patients two underwent emergency Caesarean section following the onset of labour. The remaining four patients underwent elective Caesarean section.

The measurements were performed in a room adjacent to the operating theatre to avoid delay in the commencement of the measurements. The electrical impedance of the cervical sample was measured over a range of frequencies using a single channel multi-frequency impedance measuring system utilising a four electrode method. The frequencies used ranged from 9.6 kHz to 614 kHz.

The measurements were obtained at regular intervals over approximately an hour from the time of excision of the cervical tissue.

The data was normalised using the lowest frequency measurement as the reference and the normalised impedance values were fitted to the Cole equation (Cole and Cole 1941).

The subjects were divided into term (≥ 38weeks) and preterm (< 37weeks). The ratio of extracellular to intracellular space (R/S) decreased with increasing gestation possibly indicating an increasing extracellular space in the term group. This was explained by an increase in cervical hydration with increasing gestation.

The authors accept that the sample size was too small to draw any firm conclusions but felt that further studies were warranted.

1.6.7 Summary

It is clear from this review of the role of electrical impedance measurements in obstetrics and gynaecology that while there are many situations where such measurements have shown potential, they invariably have been superseded by other investigative modalitites. In the areas of prediction of female fertility and cervical intra-epithelial neoplasia electrical impedance measurements have demonstrated greatest potential to date.

CHAPTER 2 EQUIPMENT DESIGN AND TESTING

2.1 INTRODUCTION

The design and construction of the probe is considered with particular emphasis on it's suitability to detect changes in cervical tissue. The calibration and sterilisation process for the probe is described. The reliability of the measurements at a depth where the tissue changes occur is discussed.

2.2 PROBE DESIGN

In order to measure the electrical impedance of the cervix in the *in-vivo* setting, factors such as length and diameter of the probe, electrode selection and ease of sterilisation had to be factored into the probe design.

2.2.1 Design criteria

Design criteria are determined by the site at which the measurements take place.

We decided that measurements would be taken on the cervical surface. This decision was based on the physiology of cervical ripening (section 1.2.3). The probe tips would measure 5.5 mm and 8mm in diameter, with four electrodes on their surface to measure impedance of the cervical surface. The probe was constructed to a length of 15cm for ease of use, as the length of the vagina is approximately 8cm.

Materials used for construction had to be suitable for internal use and all the materials used to construct the probe had to be biocompatible to avoid reactions with the biological tissues.

The upper 15 mm of the probe had to be both rigid to assure maximum contact with the tissue, and smooth to avoid any trauma to the cervical tissue.

2.2.2 Sterilisation of the probes

The probes were designed to be compatible with other sterilisation procedures used within both the delivery suite and the antenatal clinic. Any method of sterilisation needs to destroy all traces of infectious agents. The method chosen for sterilisation was a fluid method, so the materials used for the probe had to withstand this procedure. Prosys SM1 (formerly called Sanctimed) was choosen. A 6% solution, which was composed of didecylmethyl ethoxy-ammonium proprionate (3.0%), benzalkonium chloride (1.4%), cocopropylene diamine guanidium acetate (0.5%), acetic acid non-ionic corrosion inhibitors (0.1%) and water (95%), was used. This disinfectant was choosen because of its spectrum of activity against bacteria (***Mycobacterium tuberculosis and M. avium intracellulare, Staphylococcus aureus, Proteus mirabilis, Pseudomonas aeruginosa and Escherichia coli***), fungi (*Candida albicans*),Viruses (Hepatitis B virus and Human Immunodeficiency Virus) and Protozoa (Cryptosporidium) (Nicholoson et al 1995, Holton et al 1994). The active non-ionic detergent of the solution allowed for removal of blood and organic material from the probes. The detergent also had the advantage in having a neutral pH, it had no corrosive effect on either the metal or plastic components of the probes. The detergent also had the advantage in not containing aldehydes, it did not exhibit an unpleasant odour and was not an inhalational hazard and so was easily transportable to either the delivery suite, the fetal assessment unit or to the

antenatal clinic. This was important as the probes had to be cleaned and disinfected between each patient. Clearance for use of Prosys SMI was obtained from both the Pharmacy and Infection Control departments in Hull Royal Infirmary, Royal Hospitals NHS Trust, prior to use. The probe body was constructed to fit all the above criteria (figures 2.1 and 2.2). The cables used had to be individually screened with the screen of each coaxial cable electrically driven to minimise the effect of cable capacitance on measurement accuracy. As there had to be 4 cables (one going to each electrode) the diameter of each cable could be no more than 1.5 mm.

2.2.3 Electrode selection

The four electrodes had to be such that they fitted into the surface of each of the probe tips which were approximately 5.5 mm and 8mm in diameter respectively. The electrodes were designed to be equally spaced and at the corners of a square for ease of construction. Whilst not the optimum design, they were originally to be segmental in shape to maximise their area (fig. 2.3). However, the sharp corners of the electrodes would give high field gradients and hence a very non-uniform sensitivity. Therefore, it was decided for simplicity to construct the electrodes as a circular shape of diameter 1.5 mm. The distance between each electrode needed to be equal to or greater than the depth of tissue (fig.2.3).

Figure 2.1 5.5mm and 8mm diameter pencil probes.

basic probe design

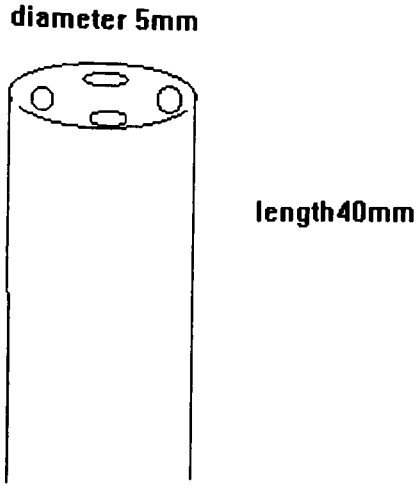

Figure 2.2 The probe design. The upper 40 mm is constructed of a rigid strong plastic. The remainder of the probe body is of stainless steel with the total length being 150 mm.

The 8mm probe was constructed in a similar manner.

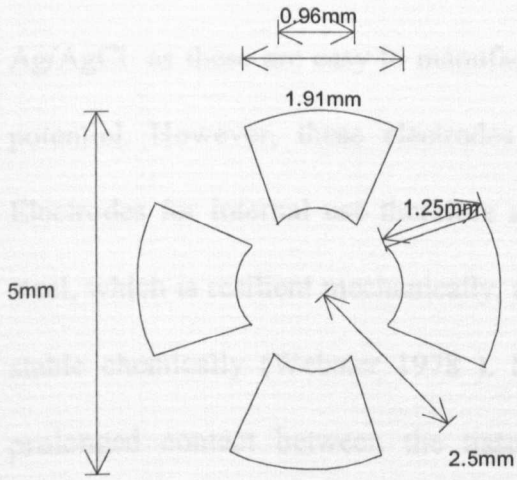

Figure 2.3 The segmental arrangement of the electrodes and sizes to be constructed for the 5.5mm probe only

The surface electrodes were constructed of suitable material for contact with biological tissue. Generally electrodes used for impedance measurements are Ag/AgCl as these are easy to manufacture in any desired shape and exhibit stable potential. However, these electrodes are fragile and could possibly be toxic. Electrodes for internal use therefore are preferably made of gold plated stainless steel, which is resilient mechanically, although softer platinum is found to be more stable chemically (Webster 1978). Solid gold was used for the electrodes, as prolonged contact between the tissue and the gold electrodes causes neither oxidation phenomena nor pollution of the tissue surface. The probe was constructed to meet all the above specifications and connected to a multi-frequency impedance meter. An input current of approximately 10 μA(p-p) was applied between two adjacent electrodes and the voltage read between the opposite pair of electrodes. The impedance meter injects current at eight frequencies in binary steps from 4.8 kHz to 614 kHz during a period of 16.7 ms. This software can be modified easily to take into account changes that are thought suitable to simplify the process of collecting data. The software records 100 values, for each of the eight frequencies, from which the mean of these values is found. In analysing the data only these eight mean values are used.

2.2.4 Spreading impedance of electrodes

The electrodes themselves will have an impedance resulting from the potential gradient set up in the tissue underneath the probe. This impedance can be calculated using the terminology shown in figure 2.4.

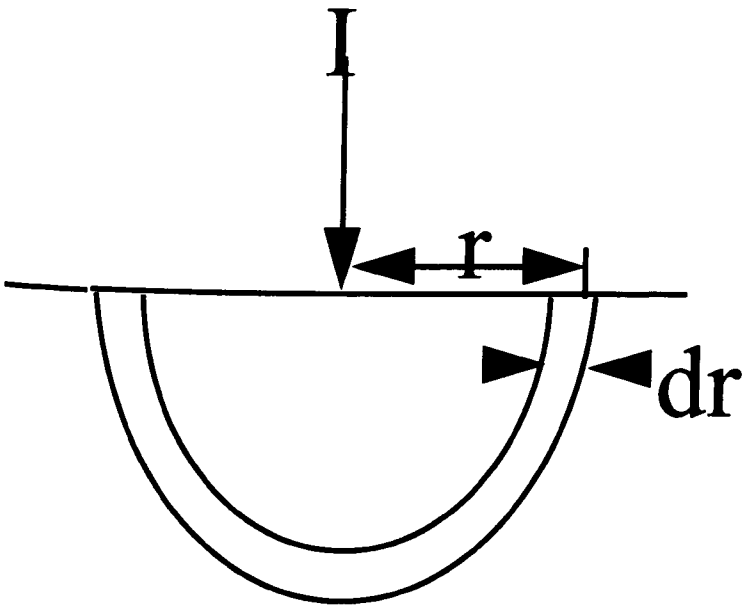

Figure 2.4 Spreading impedance of the electrodes. An electrode is positioned at point I where current is injected on the surface of tissue which is assumed to be both homogeneous and semi-infinite in extent. r = radius, dr = thickness of tissue

Consider a hemisphere of tissue of thickness *dr* at radius *r* from the electrode then the potential drop dV across the element dr is given by

$$dV = \frac{I\rho.dr}{2\pi r^2} \qquad 2.1$$

where ρ is the resistivity of the medium and I is the injected current.

Integrating from ∞ to r

$$V = \frac{\rho I}{4\pi r} \qquad 2.2$$

The potential V will rise rapidly close to the electrode so that a point electrode will have an impedance which approaches infinity. An electrode of finite area a can be modelled as a hemisphere of radius $\sqrt{(a/2\pi)}$ and hence the electrode impedance $=V/I$ will be given by:

$$V / I = \frac{\rho}{\sqrt{2\pi a}} = \text{spreading impedance,} \qquad 2.3$$

where a is the area of the electrode and $r = \sqrt{(a/2\pi)}$.

Following calibration of the probe the resistivity of cervical tissue can be calculated. Taking a value of 2 Ωm for the resistivity, we can calculate the spreading impedance for the 1.5 mm diameter electrodes as approximately 600Ω.

2.2.5 Depth sensitivity

The changes in the cervix which we wished to measure are determined by the process of effacement. Opinion is divided as to whether the process of effacement begins at the internal os and proceeds to the external os or *vice verse*. That effacement begins at the external os is supported by the fact that the cervix may contract in response to oxytocics during the latent phase of labour (Oláh 1993). The presence of such contractions appears to be a feature of the non-dilated and uneffaced cervix. Cervical contractions if observed are only seen during the first 3-4 cm dilatation. These contractions are thought to be caused by the sparse muscle content of the cervix. The net result of these contractions is a redistribution of cervical tissue which may contribute to the process of effacement (Oláh 1991). Thus effacement would occur beginning at the external os and leave the internal os the last of the tissue to be affected. In such circumstances the depth at which we could measure cervical change would be at a very superficial level. However evidence that effacement begins at the level of the internal os is supported by ultrasonographic evidence of cervical shortening associated with increasing gestation (Guzman 1996, Iams 1996) and the association of increased risk of preterm labour with a shortened cervix and funnelling of the internal os (Berghalla 1997). In such circumstances the depth at which we would need to measure cervical change would be at a much deeper level. It was postulated that cervical change

could begin at the external os particularly with the use of intra-vaginal prostaglandins.

The sensitivity of the electrode array to detect changes in resistivity decreases rapidly with depth from the array. This depth sensitivity can be calculated from the Geselowitz Lead theory (Geselowitz 1971).

This describes the change in transfer impedance ΔZ resulting from a change Δg in conductivity of a particular region of a volume conductor using four electrode measurements and is given by:

$$\Delta Z = -\Delta g \int L_{\varphi} \cdot L_{\psi} \, dv \qquad 2.4$$

L_{φ} and L_{ψ} are the Lead fields associated with the two ports to measure ΔZ (Geselowitz, 1971). The Lead field is the electric field that would exist at a point when unit current is injected.

Geselowitz states that information about the internal conductivity of an insulated volume conductor can be gained from impedance measurements at its surface. By selecting various positions for the placement of surface electrodes, changes in conductivity over time can be measured and it should be possible to develop an arrangement for which the mutual impedance is selective for and sensitive to a particular region. The transfer impedance should be proportional to the dot product of the transfer impedance's associated with the current and voltage terminals.

For the case of a linear volume conductor surrounded by an insulator, (fig. 2.5), a current I_φ injected into the conductor at AB will produce a voltage φ_{CD} across electrodes C and D. Due to the reciprocity theorem, it also follows that a current I_ψ injected into CD will give rise to a voltage ψ_{AB} . The mutual impedance can be written

$$Z = \frac{\varphi CD}{I_\varphi} = \frac{\Psi AB}{I_\Psi} \qquad 2.5$$

The change in mutual impedance ΔZ, or sensitivity can be given by equation 2.6

$$\Delta Z = \frac{\Delta \varphi_{AB}}{I_\varphi} = -\Delta g \int \frac{\nabla(\varphi + \Delta\varphi)}{I_\varphi} \bullet \frac{\nabla_\Psi}{I_\Psi} dv \qquad 2.6.$$

where Δg is the change in conductivity, $\Delta\varphi$ is the resultant change in scalar potential associated with I_φ , with dv being the volume over which the conductivity change occurs (Erol 1996). If we assume $\Delta\varphi$ is small, it can be ignored, making the equation linear.

How the sensitivity of the probe changes at different depths from the array is dependent on the separation of the drive and receive electrodes. For our probe the electrode array is circular and so the geometry of Geselowitz theory has to be adapted for this circular array. The depth sensitivity is calculated at a point that can be drawn as a midline from the centre of the circular array (Figs.2.6,2.7).

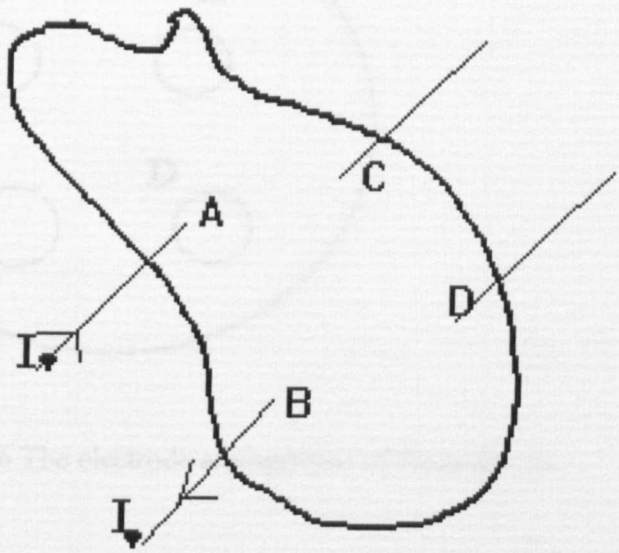

Figure 2.5 Electrodes on the surface of an insulated semi-infinite conductor. Current is injected into electrode pair A & B which produces a potential across electrodes C & D

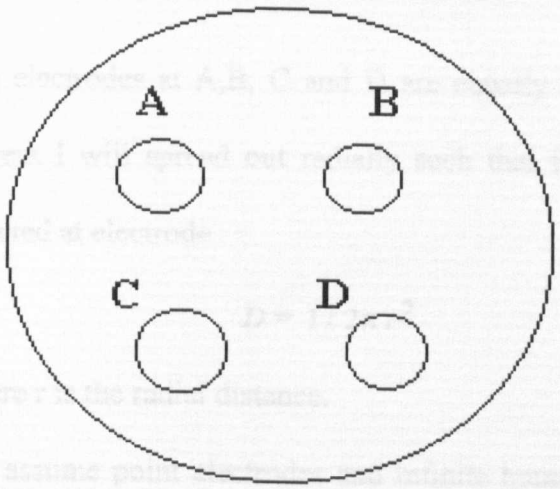

Figure 2.6 The electrode arrangement of the probe tip.

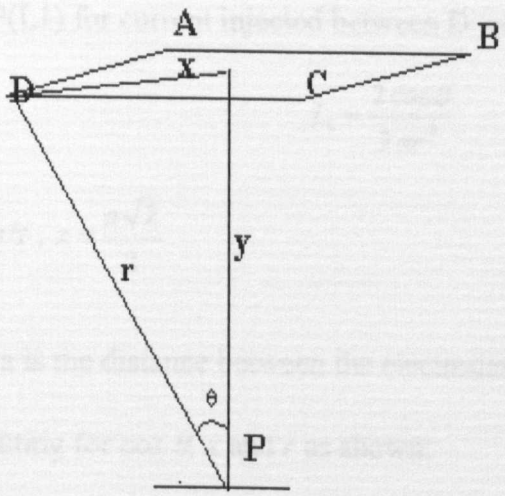

Figure 2.7 Shows the point at which the depth sensitivity is calculated.

The electrodes at A,B, C and D are equally spaced on a circle of radius x. The current I will spread out radially such that the current density from a current I injected at electrode

$$D = I / 2\pi r^2 \qquad 2.7$$

where r is the radial distance.

We assume point electrodes and infinite homogeneous geometry. The component parallel to the surface will be:

$$= \frac{I}{2\pi r^2}.\cos\theta \qquad 2.8$$

for I injected at C this component will be the same such that the electric field at point P(L1) for current injected between D and C is:

$$L_1 = \frac{2\cos\theta}{2\pi r^2} \qquad 2.9$$

$\cos\theta = x/r$, $x = \frac{a\sqrt{2}}{2}$

where a is the distance between the electrodes and $r = (y^2 + x^2)^{\frac{1}{2}}$

substituting for $\cos\theta$, x and r as shown:

$$L_1 = \frac{2x}{2\pi r^3} \qquad 2.10$$

$$= \frac{a\sqrt{2}}{2\pi(y^2 + (\frac{a\sqrt{2}}{2})^2)^{\frac{3}{2}}} \qquad 2.11$$

The electric field at P for current injected between A and B will be the same $L_1 = L_2$ from Geselowitz theory assuming $\Delta z \propto L_1 \cdot L_2$

therefore :

$$\Delta Z \propto (L_1)^2 \qquad 2.12$$

$$\Delta Z \propto \frac{2a^2}{4\pi^2 (y^2 + \frac{2a^2}{4})^3} \qquad 2.13$$

By using equation 2.13, the sensitivity can be evaluated, and expressed in terms of the drive separation (= receive separation).

2.2.6. Calibration

The initial calibrations were performed in the University of Sheffield department of Medical Physics and Clinical Engineering at the Royal Hallamshire Hospital. The probes were calibrated in saline of conductivity 0.95mS/cm (10.52Ω). The frequencies used ranged from 4.8kHz to 614kHz in 8 steps.

For the plug calibration using the RSC circuit (Fig.1.6) the theoretical values at gain 8 for R=S= 220Ω and C =3.3n were as follows:

2.81 3.03 3.64 4.55 5.15 5.34 5.43 5.44

with actual values at gain 8:

2.74 3.05 3.68 4.55 5.20 5.38 5.43 5.35.

Calibration was performed by placing the probes in one tenth normal saline prior to taking any readings. This was carried out before any clinical work was done to check for any drifts in voltage values.

Calibrations so far have resulted in there being a 10% difference in values.

2.2.7. Summary

In this section issues associated with the design of the probes such as electrode selection, depth sensitivity, spreading impedance of the electrodes, and calibration have been discussed. Issues associated with sterilisation of the probes in the clinical setting are also considered.

2.3 INTER - OBSERVER VARIABILITY STUDY

2.3.1 Aim of the study

The aim of this study was to ascertain the reproducibility of the measurements when the readings were taken by different observers. If electrical impedance measurements are to be of clinical value then they need to be reproducible.

2.3.2 Patients and methods

The patients were recruited from both the antenatal and post-natal wards and clinics. Each gave written informed consent prior to undergoing the measurements. The measurements were taken in the standard manner by placing the probe on the surface of the cervix and passing a current of 10 μA between the adjacent pair of electrodes and measuring the resulting potential between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the average calculated. Only readings taken at the 4.8 kHz frequency were used for the analysis. The measurements were initially taken by myself and these were followed by readings taken by a midwife under my supervision. Initially the midwife had observed me taking the readings and the readings used in this analysis were those taken once the midwife was confident with her technique. In all 18 patients participated in this study.

The analysis of the results is expressed as percentage change between:

1. My highest reading and the midwife's highest reading, giving the minimum difference.

2. My lowest reading and the midwife's highest reading, giving the maximum difference.

3. The mean of my readings and the mean of the midwife's reading, giving the percentage difference of the mean readings.

2.3.3 Results

The antenatal group consisted of 10 patients with a mean gestation of 33 weeks (range 24 - 39 weeks). The mean minimum difference was 6.6% (range 0.9% - 22%), with a mean maximum difference of 42.5% (range 17% - 76%) and a mean difference of the means of 16% (range 8% - 43%) (table 2.1).

The post-natal group consisted of 8 patients with a mean of 13.5 days (range 2 - 49 days) post delivery. The mean minimum difference was 13.2% (range 0.3% - 25%), with a mean maximum difference of 39.6% (range 13% - 60%) and a mean difference of the means of 22% (range 2% - 46%) (table 2.2).

GESTATION (WEEKS)	MINIMUM DIFFERENCE (%)	MAXIMUM DIFFERENCE (%)	DIFFERENCE OF THE MEANS (%)
30	6.0	32.0	9.0
31	1.9	17.0	8.0
24	10	21.0	15.0
24	0.9	38.0	9.0
33	10	44.0	20.0
30	9.8	76.0	18.0
24	0.9	34.0	20.0
30	22	60.0	43.0
38	2.0	52.0	9.0
39	3.0	51.0	9.0

Table 2.1 Inter-observer variability of the antenatal patients. The gestational age, minimum percentage difference, maximum percentage difference and percentage difference of the means of the electrical impedance readings, are shown.

DAYS POST DELIVERY	MINIMUM DIFFERENCE (%)	MAXIMUM DIFFERENCE (%)	DIFFERENCE OF THE MEANS (%)
3	0.3	53.0	8.0
3	25.0	31.0	30.0
4	24.0	60.0	28.0
3	4.4	38.0	9.0
2	16.0	33.0	26.0
2	26.0	32.0	27.0
49	0.5	57.0	46.0
42	9.0	13.0	2.0

Table 2.2 Inter-observer variability of the post-natal patients. The number of days post delivery, minimum percentage difference, maximum percentage difference and percentage difference of the means of the electrical impedance readings, are shown.

2.3.4 Discussion

This study highlights at times large inter-observer differences when comparing individual readings as attested to by the differences seen in both the minimum and maximum differences as shown in tables 2.1 and 2.2. However when the difference of the mean readings are compared then the inter-observer variability is much tighter. Hence the reason for taking more than one set of readings in all patients.

The inter-observer variability is in part explained by the learning curve for the midwife. In my initial sets of readings the number of unacceptable readings was in the region of 20%. These were most often due to slippage of the probe and using too low a gain. However following the 30th set of readings I found that the number of unacceptable readings was in the region of 1%. Despite the midwife observing numerous sets of readings prior to commencing taking readings herself and despite the readings which she took as practice readings, she was nevertheless still on the learning curve when we performed this study. It would also have been interesting to assess the inter-observer variability with other medical staff of varying levels of experience to ascertain who should take these readings if the test were to be of clinical value.

The inter-observer variability could be in part also explained by the applied pressure of the probe on the cervix. This is an area we have still to address and will be incorporated in future studies.

The differences seen between the difference of the means between the antenatal and post-natal patients is explained by the increased technical difficulty in taking the readings in the post-natal period, particularly in those patients who had a vaginal delivery. The amount of lochia played a large part in these technical difficulties, particluarly in visualisation of the cervix and more importantly in patient unease if the loss was large.

2.3.5 Conclusion

This study has demonstrated that while the inter-observer variability can be large when individual readings are assessed, it can be substantially minimised if mean readings are used for analysis.

2.3.6 Summary

This study shows acceptable inter-observer variability when the mean readings are used for analysis. However it is limited by its size, and by the fact that only myself and a midwife compared our results.

Further work will be required to assess the effect of the experience of the personnel taking the readings and the effect of the pressure of the probe on the cervix when the readings are recorded.

2.4 INTRA-OBSERVER VARIABILITY STUDY

2.4.1 Aim of the study

The aim of this study was to determine the intra-observer variability between readings taken at the same point on the cervix.

2.4.2 Patients and methods

The patients were recruited from both the antenatal and post-natal wards and clinics. Each gave written informed consent prior to undergoing the measurements. The measurements were taken in the standard manner by placing the probe on the surface of the cervix and passing a current of 10 μA between the adjacent pair of electrodes and measuring the resulting potential between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the average calculated. Each patients had at least four sets of readings. Only readings taken at the 4.8 kHz frequency were used for the analysis. For the purpose of this study the percentage difference between the lowest and highest recorded resistivity measurements were determined.

Prior to commencing this study, it was agreed in conjunction with our medical physics colleagues that an intra-observer variability in the region of 10%-15% would be considered acceptable.

2.4.3 Results

The study included 100 patients who had readings recorded with both the 5.5mm and 8mm probes. The mean percentage difference between the lowest and highest resistivity readings using the 5.5mm probe was 6.89% (range 0.3%-28.6%)and 8.29% (range 0.2%-47.0%) using the 8mm probe. The 10% intra-observer variability the set prior to the study was achieved in 80% of cases using the 5.5mm probe with only 6% of cases showing a difference of ≥15% (Figure 2.8). The 10% level was achieved in 76% of cases using the 8mm probe, with 10% of cases showing a difference of ≥15% (Figure 2.9). In all cases where the resistivity percentage difference was ≥15% the probe was re-applied to the cervix between each set of readings.

2.4.4 Discussion

The results of this study were reassuring in that 94% and 90% of cases using the 5.5mm and 8mm probes respectively were within the 15% intra-observer variability that was considered acceptable for the purposes of the study.

The re-application of the probe between readings led to wide fluctuations in the readings. As a result it was decided to accept only readings that were recorded without re-applying the probes to the cervix. A variety of reasons were considered as to why the intra-observer variability should have been increased when the probes

were re-applied. Alterations in readings due to the pressure applied to the cervix by the probe could explain these phenomena. However all the readings were performed by the same operator for the purposes of this study.

An alternative explanation would be that in re-applying the probe, its positioning with respect to the cervix is altered and so lead to the difference in the readings. Clearly further methodological work is required to clarify such matters.

2.4.5 Summary

The system performed well in that the intra-observer variability was ≥15% in only 6% and 10% of cases for the 5.5mm and 8mm probes respectively. As the results were heavily influenced by the re-application of the probes it was decided for uniformity of the measurements only readings recorded when the probes were not re-applied to the cervix would be considered for analysis.

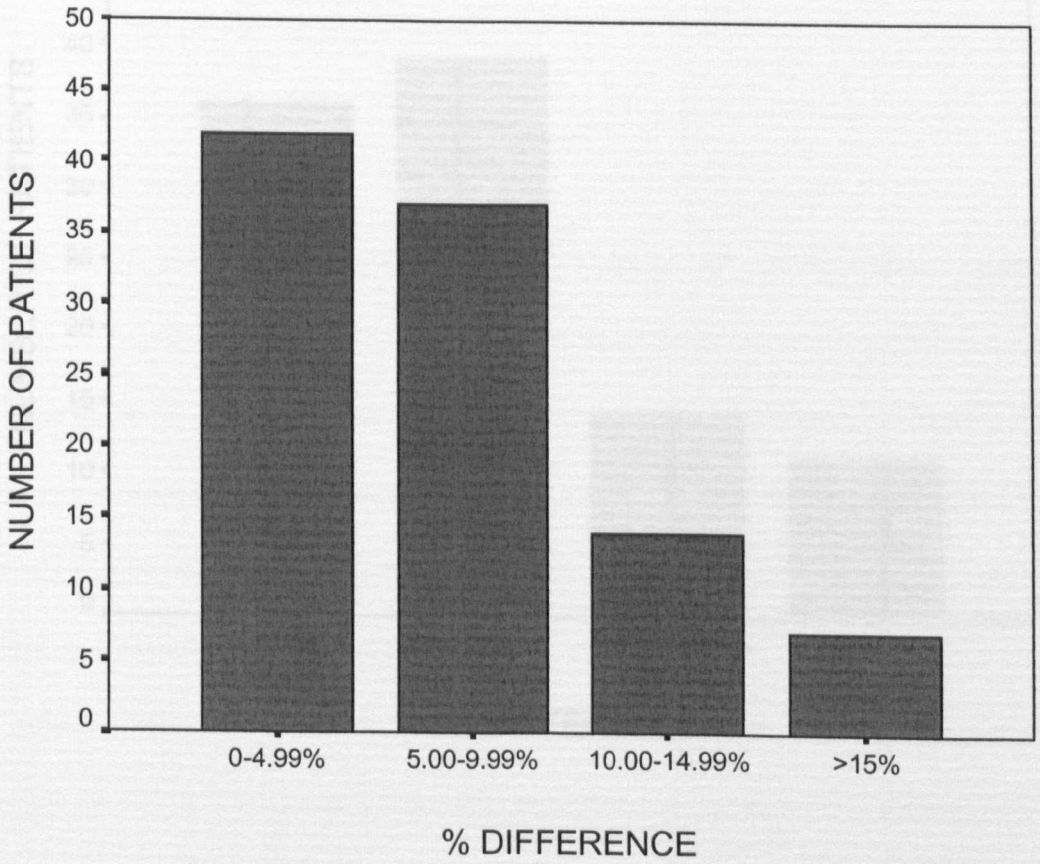

Figure 2.8 Number of patients categorised in terms of percentage difference between the highest and lowest resistivity readings using the 5.5mm probe.

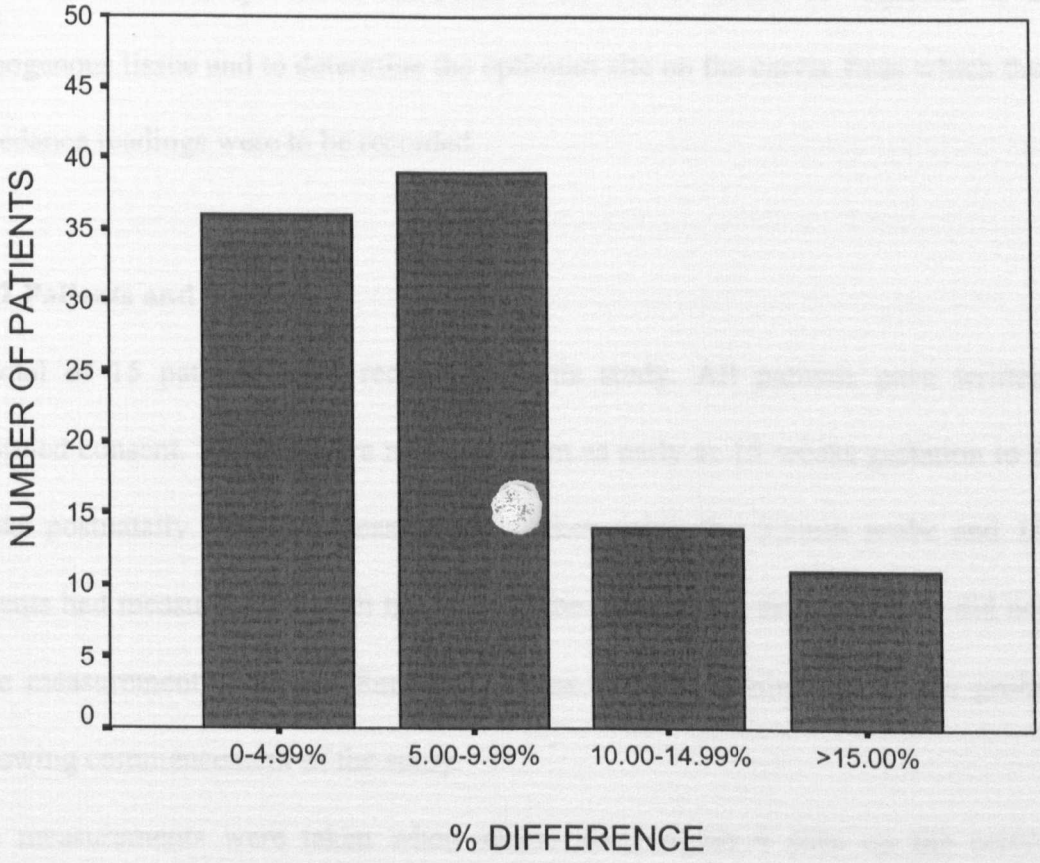

Figure 2.9 Number of patients categorised in terms of percentage difference between the highest and lowest resistivity readings using the 8mm probe.

2.5 MULTIPLE SITE STUDY

2.5.1 Aim of the study

The aim of the study was to ascertain if the cervix could be regarded as a homogenous tissue and to determine the optimum site on the cervix from which the impedance readings were to be recorded.

2.5.2 Patients and methods

A total of 15 patients were recruited to this study. All patients gave written informed consent. Patients were recruited from as early as 15 weeks gestation to 6 weeks postnatally. All had measurements taken using the 5.5mm probe and 11 patients had measurements with the 8mm probe. The reason that 4 patients did not have measurements with the 8mm probe was that we obtained the 8mm probe following commencement of the study.

The measurements were taken when access allowed, on 4 sites on the cervix namely, 3, 6, 9 and 12 o'clock. Transfer impedance measurements were made at 8 different frequencies using the 5.5mm and 8mm pencil probes, each with four gold electrodes mounted flush with the face of the probe. The probe was placed on the surface of the cervix and did not enter the substance of the cervical tissue. A current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential was measured between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the

average calculated. Only readings taken at the 4.8 kHz frequency were used for the analysis.

2.5.3 Results

The changes in mean extracellular resistivity noted between readings taken on the anterior and posterior lips of the cervix, using the 5.5mm probe, are shown in figure 2.10. The extracellular resistivity is shown to rise in seven of the cases, with no change in two cases and a further fall in the remaining six cases. In those cases where the extracellular resistivity demonstrated a rise between the anterior and posterior lip of the cervix, the cervix was deemed unfavourable. Where there was no change between the extracellular resistivity measurements, one case had recently delivered normally and the other had a favourable cervix at 38 weeks gestation. Where the extracellular resistivity decreased between the anterior and posterior lips one case was in early labour, four cases, while having an unfavourable cervix nevertheless had a history of previous idiopathic preterm deliveries in the past, and the final case was a post-natal case at six weeks post normal delivery.

Overall the changes seen in mean intracellular resistivity between the anterior and posterior lips of the cervix were in the opposite direction to that demonstrated by the mean extracellular resistivity (figures 2.10, 2.11), with the following exceptions, three cases where the extracellular resistivity decreased and the intracellular resistivity increased, two cases where the extracellular resistivity demonstrated no change and the intracellular resistivity decreased, and two cases

where the extracellular resistivity decreased and the intracellular resistivity decreased.

Whilst the changes in the mean intracellular resisitivity were in general in the opposite direction to that of the mean extracellular resistivity, the differences noted were less (Table 2.3).

The results using the 8mm probe were almost identical in the changes noted between the anterior and posterior lips of the cervix using the 5.5mm probe. Data are only available for 11 cases using the 8mm probe. In only 3 cases were the changes in extracellular and intracellular resistivity in the same direction.

The changes between the anterior and posterior lips of the cervix are shown in table 2.3 for the 5.5mm probe and table 2.4 for the 8mm probe.

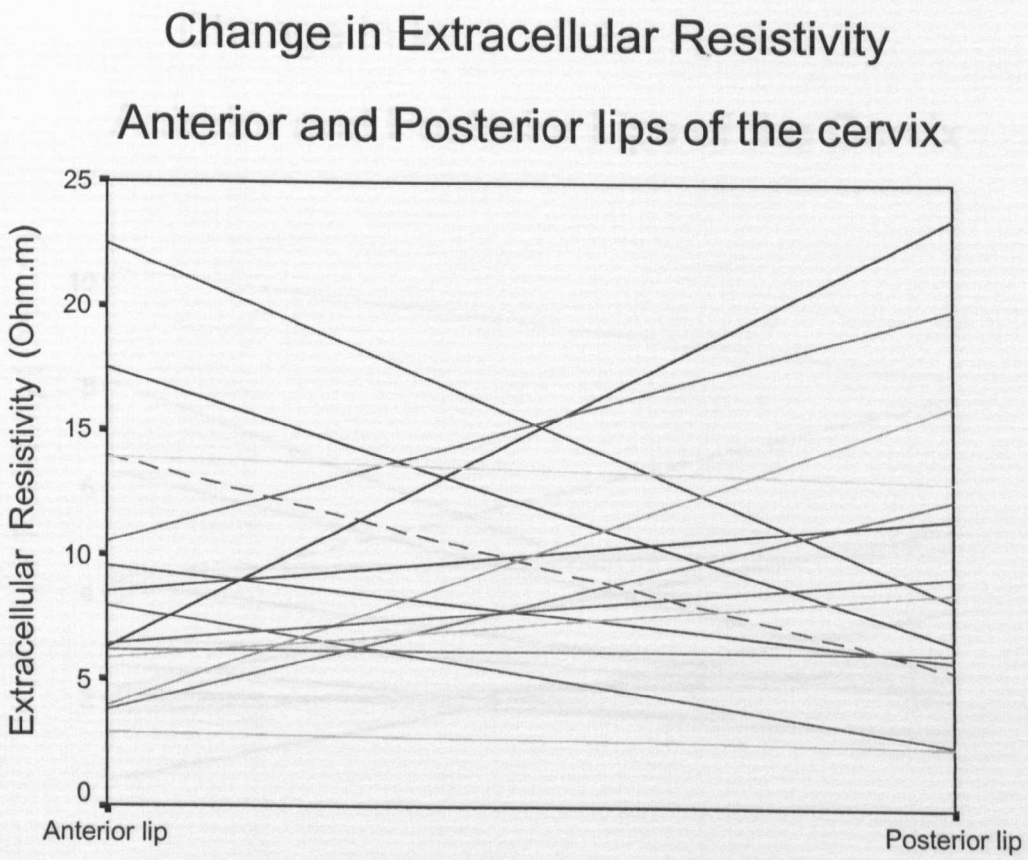

Figure 2.10 Change in resistivity between anterior and posterior lips of the cervix.

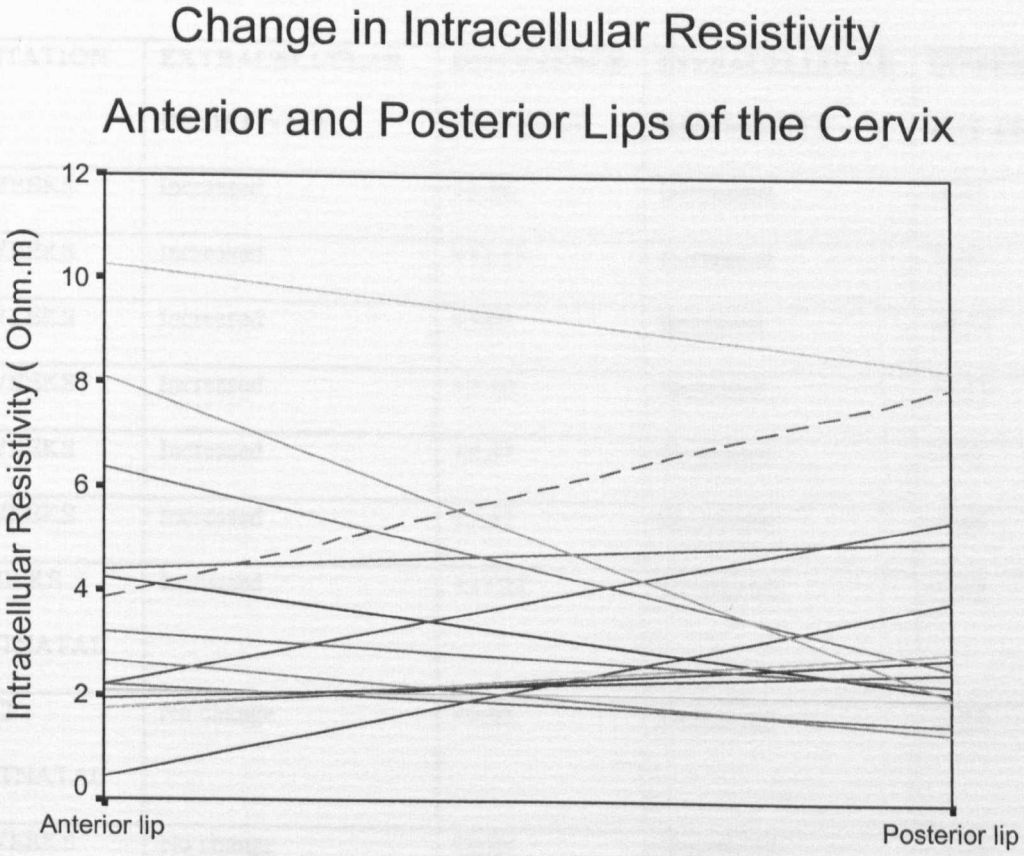

Figure 2.11 Change in intracellular resistivity between anterior and posterior lips of the cervix.

GESTATION	EXTRACELLULAR RESISTIVITY	DIFFERENCE ANT-POST	INTRACELLULAR RESISTIVITY	DIFFERENCE ANT-POST
40 WEEKS	Increased	+2.82	Decreased	-1.02
40 WEEKS	Increased	+12.15	Decreased	-6.07
39 WEEKS	Increased	+3.07	Increased	+0.57
33 WEEKS	Increased	+2.70	Increased	+1.13
29 WEEKS	Increased	+8.47	Decreased	-3.77
25 WEEKS	Increased	+9.47	Decreased	-0.69
6 WEEKS POSTNATAL	Increased	+17.27	Decreased	-2.12
Day 2 POSTNATAL	No change	<0.05	Decreased	-1.32
38 WEEKS	No change	<0.05	Decreased	-1.97
40 WEEKS	Decreased	-0.87	No change	<0.05
37 WEEKS	Decreased	-10.95	Increased	+1.04
33 WEEKS	Decreased	-3.69	Increased	+3.22
31 WEEKS	Decreased	-14.22	Increased	+3.44
15 WEEKS	Decreased	-5.48	Decreased	-0.62
6 WEEKS POSTNATAL	Decreased	-8.46	Decreased	-4.09

Table 2.3 Comparison of the changes in extracellular and intracellular resistivity between anterior and posterior lips of the cervix using the 5.5mm probe.

GESTATION	EXTRACELLULAR RESISTIVITY	DIFFERENCE ANT-POST	INTRACELLULAR RESISTIVITY	DIFFERENCE ANT-POST
40 WEEKS	Increased	+4.61	Decreased	-3.49
40 WEEKS	Increased	+7.68	Decreased	-6.03
40 WEEKS	Increased	+0.55	Decreased	-7.32
39 WEEKS	Increased	+1.81	Decreased	-0.23
38 WEEKS	Increased	+1.19	No change	<0.05
37 WEEKS	Decreased	-7.53	Increased	+1.66
33 WEEKS	Increased	+0.38	Increased	+0.12
33 WEEKS	Increased	+2.90	Decreased	-0.22
15 WEEKS	Decreased	-4.37	Increased	+2.47
DAY 2 POST-NATAL	Increased	+0.32	Increased	+2.63
6 WEEKS POST-NATAL	Decreased	-1.51	Decreased	-0.22

Table 2.4 Comparison of the changes in extracellular and intracellular resistivity between anterior and posterior lips of the cervix using the 8mm probe.

2.5.4 Discussion

This study demonstrates that the cervix appears to be heterogeneous in its consistency. It appears that there is an increase in extracellular resistivity between the anterior and posterior lips of the cervix. This difference is greater the more unfavourable the cervix and is reversed when the cervix is favourable. The exception to this is seen in those patients with a past history of idiopathic pre-term labour. In such cases it could be postulated that the cervical tissue is different from normal and so contributes to the idiopathic preterm labour. If this is the case then there is a potential for electrical impedance measurements to identify those at increased risk of idiopathic preterm labour. This would require a study of patients being admitted with threatened preterm labour, comparing those who subsequently deliver preterm with those who settle and deliver at term.

The intracellular resistivity tended to change in the opposite direction to the extracellular resistivity as we expected, with an increase in intracellular resistivity and a concomitant decrease in extracellular resistivity with increasing cervical hydration.

It is obvious that there are many confounding variables in these results. The role of parity and gestation is examined in more detail in Chapter 3.

Technically it is more difficult to acquire electrical impedance measurements on the posterior lip of the cervix. This is due to the position of the cervix. The cervix is often posterior prior to the onset of labour and therefore difficult to locate using a Cusco speculum. In addition achieving good contact between the posterior lip of

the cervix and the face of the probe is difficult. The other difficulty lies in the increased vaginal secretions in pregnancy and the issue of slippage of the probe when taking the measurements.

It may well be that the differences noted between the anterior and posterior cervical lips could be explained by the technical difficulties encountered in acquiring the readings rather than by true physiological differences.

Following this albeit small study we decided that to ensure consistent results that we would only take readings from the anterior lip of the cervix. We accept that this strategy could lead to bias in our results, but feel that the consistency of the results outweigh this problem. Clearly a larger study is required to clarify the situation.

2.5.5 Summary

This study highlights differences between readings taken from the anterior and posterior lips of the cervix. It is not clear whether these differences are due to real physiological difference or merely due to the increased technical difficulty in acquiring readings from the posterior lip of the cervix. In order to ensure consistency, we chose to take all our subsequent readings from the anterior lip of the cervix.

2.6 CHAPTER SUMMARY

In this chapter issues concerning the design of the probes were discussed, with particular emphasis on electrode selection, depth of sensitivity, the spreading impedance of the electrodes, the calibration and finally the issues associated with sterilisation of the probes in the clinical setting.

The inter-observer variability study aimed to determine the reproducibility of the impedance readings when recorded by different personnel. A total of 18 patients were recruited for this study. The study highlighted the value of recording more than one reading and using the mean value for analysis, as these appeared more reproducible. The study is limited by its small sample number and by the fact that the midwife who took the readings under supervision was still on the learning curve with regard to the technique. The issues surrounding slippage of the probe whilst taking the readings and the effect of pressure of the probe on the cervix were discussed. The increased difficulty in recording reading from post-natal patients was also addressed.

The intra-observer study of 100 patients highlighted an acceptable variability with 94% and 90% of readings being within 15% of the highest v lowest recorded resistivity for the 5.5mm and 8mm probes respectively. The poor reproducibility of measurements when the probes were re-applied was discussed.

The multiple site study set out to determine the degree of homogeneity of the cervix. Readings on the anterior and posterior lips of the cervix differed greatly. But because of the small sample size in this study, it was not possible to determine whether these changes were due to technical difficulties in obtaining the readings or due to true physiological change.

Following these studies in order to ensure uniformity in results it was concluded that;

1. All readings used for analysis would be recorded by the same operator.
2. All readings would be taken from the anterior lip of the cervix at the 12 o clock position.
3. All readings used for analysis would be a mean of the recorded readings on that patient.
4. The probes would not be re-applied during the recording of the measurements.

CHAPTER 3 THE EFFECT OF GESTATIONAL AGE, MATERNAL AGE AND PARITY ON ELECTRICAL IMPEDANCE MEASUREMENTS OF THE PREGNANT CERVIX

3.1 INTRODUCTION

It is postulated that whilst the cervix is a dynamic structure, there is little change in its hydration index prior to term (Oláh 1994). Therefore it would be expected to find relatively stable electrical impedance measurements during pregnancy with a decrease in extracellular resistivity and an increase in intracellular resistivity with the onset of the ripening process. This would reflect a fluid shift from the intracellular space into the extracellular space, which is associated with the ripening process (Uldjberg et al 1983).

There is no evidence to suggest that maternal age per se should influence the cervical ripening process. However as electrical impedance measurements had not previously been investigated in pregnancy then an assessment of the effect of maternal age on the impedance readings was required. Similarly an assessment of the effect of parity on the readings was also required.

This chapter aims to address these putative influences on the cervix and thus on the electrical impedance readings.

3.2 METHODS

This study represents a combination of data recorded from the induction of labour study and the longitudinal study. All patients gave written informed consent prior to participating in either of the above studies. The measurements were taken in the standard manner by placing the probe on the surface of the cervix and passing a current of 10 μA between the adjacent pair of electrodes and measuring the resulting potential between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix, 100 sets were recorded and the average calculated. Only readings taken at the 4.8 kHz frequency were used for the analysis. All measurements were recorded from the anterior lip of the cervix at the 12 o' clock position and by the same operator. Using the 5.5mm probe a total of 260 sets of measurements were recorded with a total of 213 sets of measurements using the 8mm probe. Extracellular resistivity and intracellular resistivity measurements used in the study were all means of at least three sets of measurements.

3.3 RESULTS

A total of 260 mean readings were recorded using the 5.5mm probe. The mean extracellular resistivity was 8.93Ωm (range 1.53-25.62Ωm), with a mean intracellular resistivity of 4.34Ωm (range 0.30-21.13Ωm). The mean gestational age was 35.1 weeks (range 14-42 weeks) with a mean maternal age of 29.1years (range 16-46 years) and the mean parity being 1.4 (range 0-5).

Statistically significant correlation's were demonstrated, correlating extracellular resistivity with intracellular resistivity (Pearson correlation coefficient -0.3981, $p<0.01$), extracellular resistivity with gestation (Pearson correlation coefficient 0.209, $p<0.01$) and extracellular resistivity with parity (Pearson correlation coefficient -0.136, $p<0.05$). No statistically significant correlation was seen comparing extracellular resistivity with maternal age. Again statistically significant correlation's were demonstrated, correlating intracellular resistivity with gestation (Pearson correlation coefficient -0.216, $p<0.01$) and correlating maternal age and parity (Pearson correlation coefficient 0.514, $p<0.01$).

A total of 213 mean readings were recorded using the 8mm probe. The mean extracellular resistivity was 5.72Ωm (range 1.96-20.66Ωm), with a mean intracellular resistivity of 2.75Ωm (range 0.25-10.09Ωm). The mean gestational age was 34.15 weeks (range 14-42 weeks) with a mean maternal age of 29.04 years (range 16-46 years) and the mean parity being 1.4 (range 0-5).

Statistically significant correlation's were seen between extracellular resistivity and intracellular resistivity (Pearson correlation coefficient -0.419, $p<0.01$) and maternal age and parity (Pearson correlation coefficient 0.503, $p<0.01$).

Scattergrams of extracellular resistivity versus gestational age, maternal age and parity are charted in figures 3.1, 3.3, 3.5 and 3.2, 3.4 and 3.6 for the 5.5mm probe and 8mm probe respectively. Similar scattergrams are shown for intracellular resistivity versus gestational age, maternal age and parity (figures 3.7, 3.9, 3.11 and 3.8, 3.10 and 3.12 for the 5.5mm probe and 8mm probe respectively).

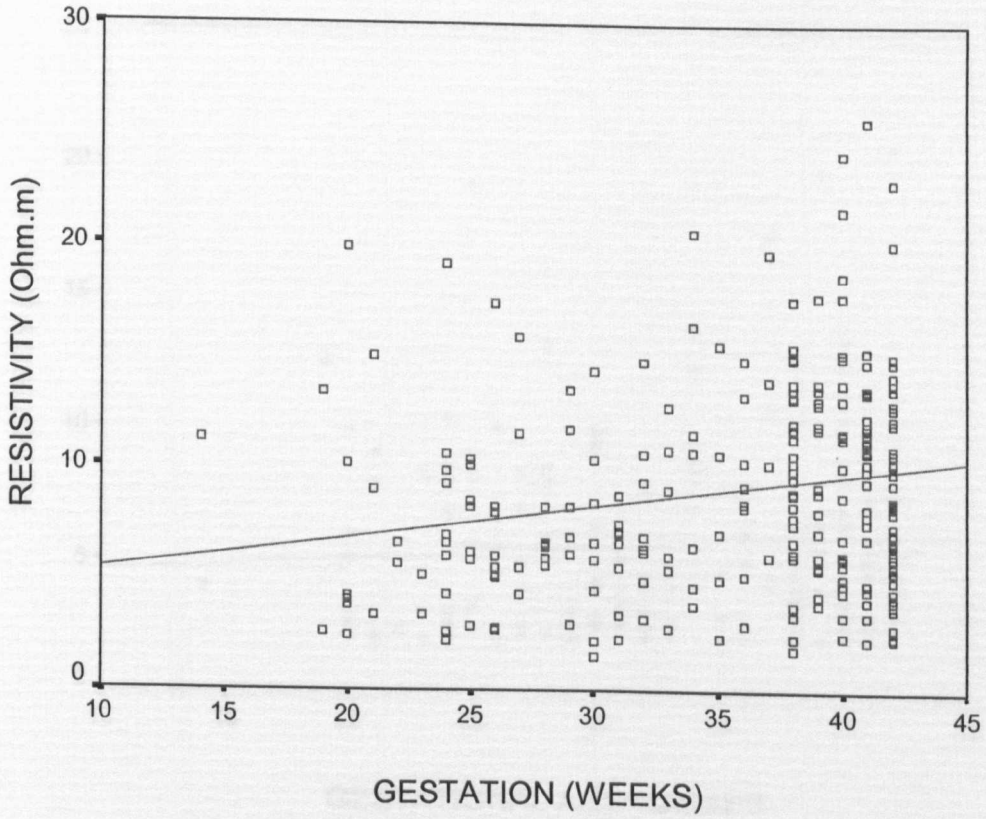

Figure 3.1 A comparison of resistivity versus gestation using the 5.5mm probe. The best fit line is superimposed.

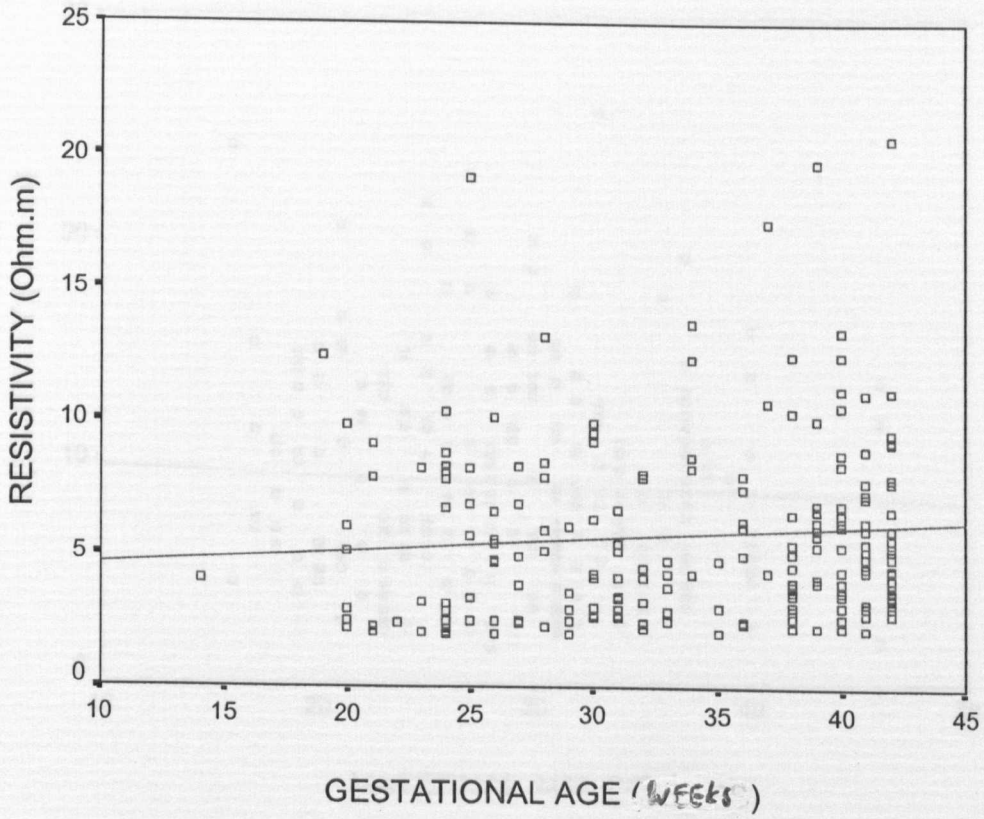

Figure 3.2 A comparison of resistivity versus gestation using the 8mm probe. The best fit line is superimposed.

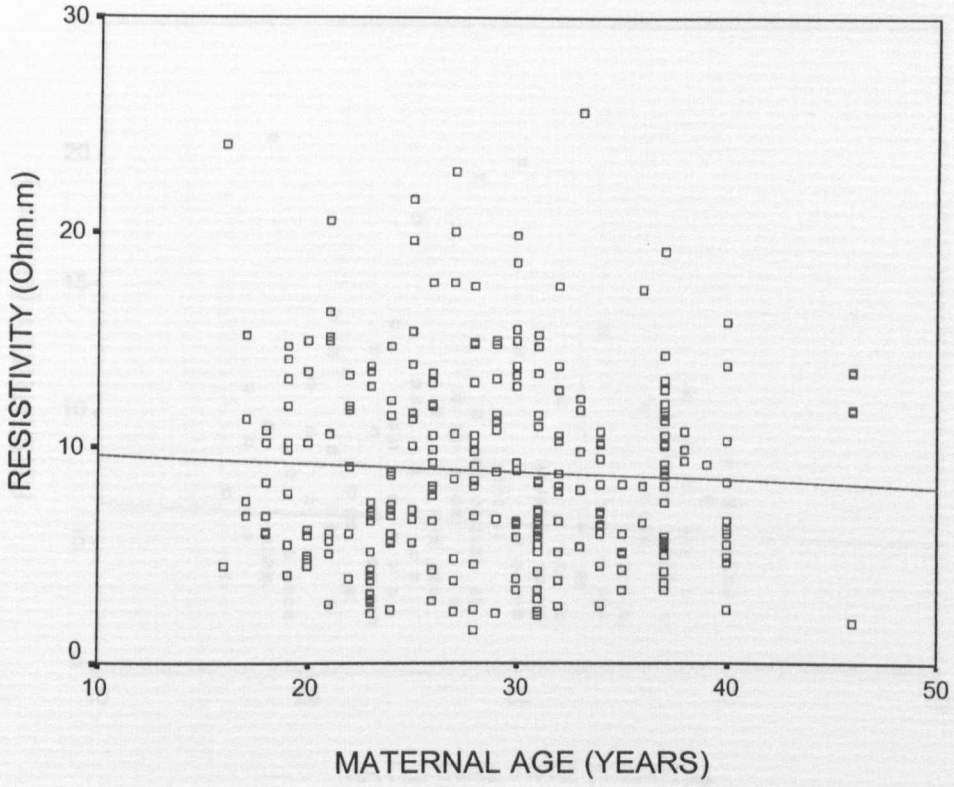

Figure 3.3 A comparison of resistivity versus maternal age using the 5.5mm probe. The best fit line is superimposed.

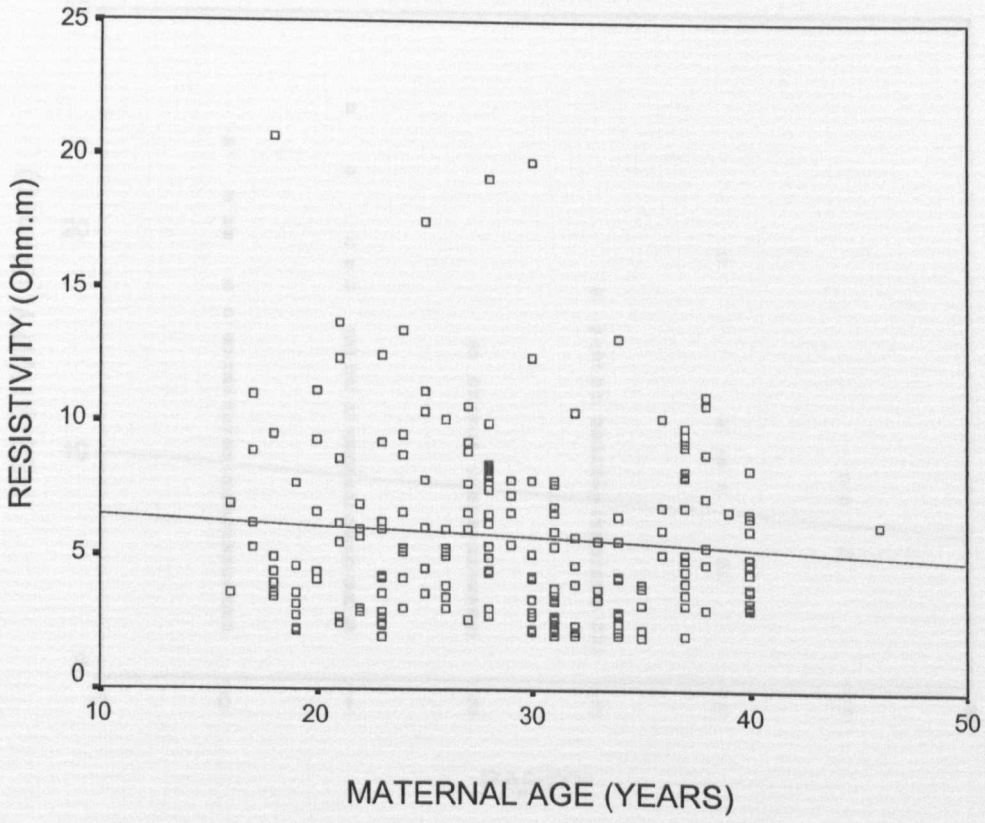

Figure 3.4 A comparison of resistivity versus maternal age using the 8mm probe. The best fit line is superimposed.

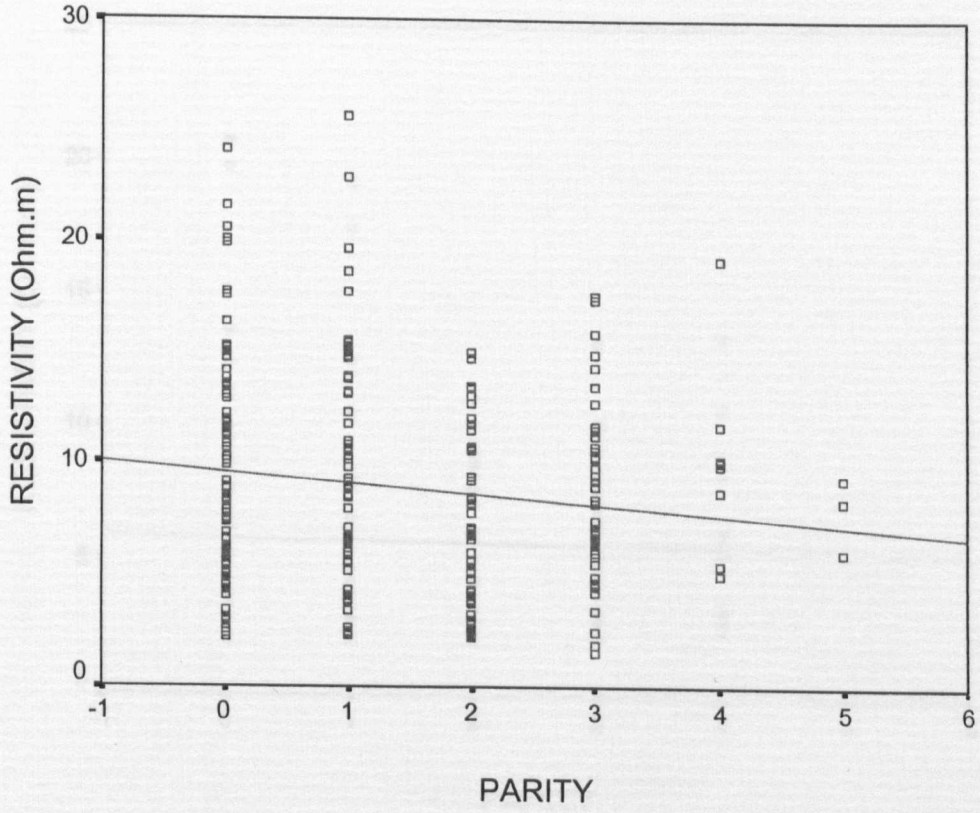

Figure 3.5 A comparison of resistivity versus parity using the 5.5mm probe. The best fit line is superimposed.

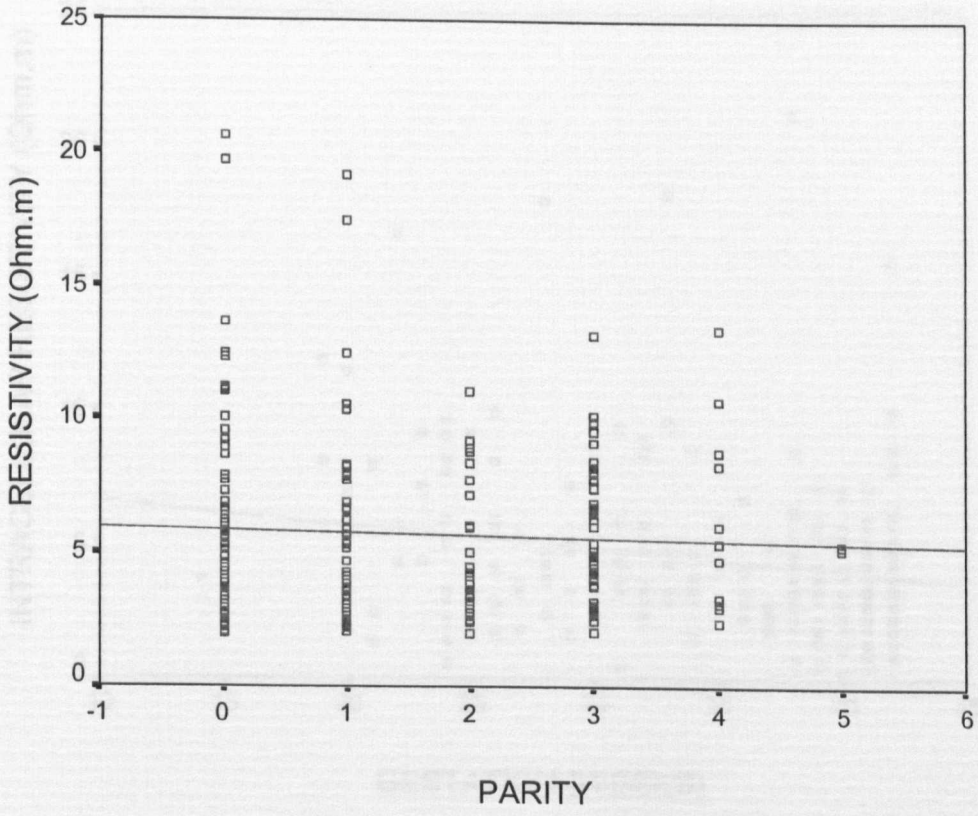

Figure 3.6 A comparison of resistivity versus parity using the 8mm probe. The best fit line is superimposed.

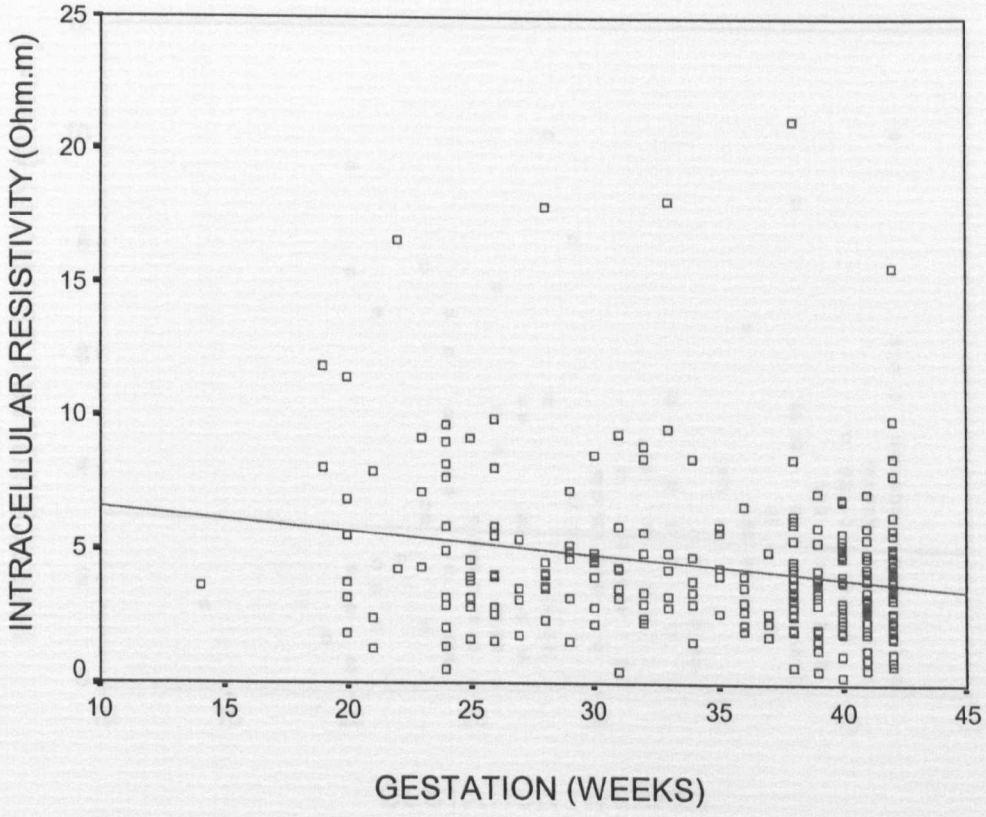

Figure 3.7 A comparison of intracellular resistivity versus gestational age using the 5.5mm probe. The best fit line is superimposed.

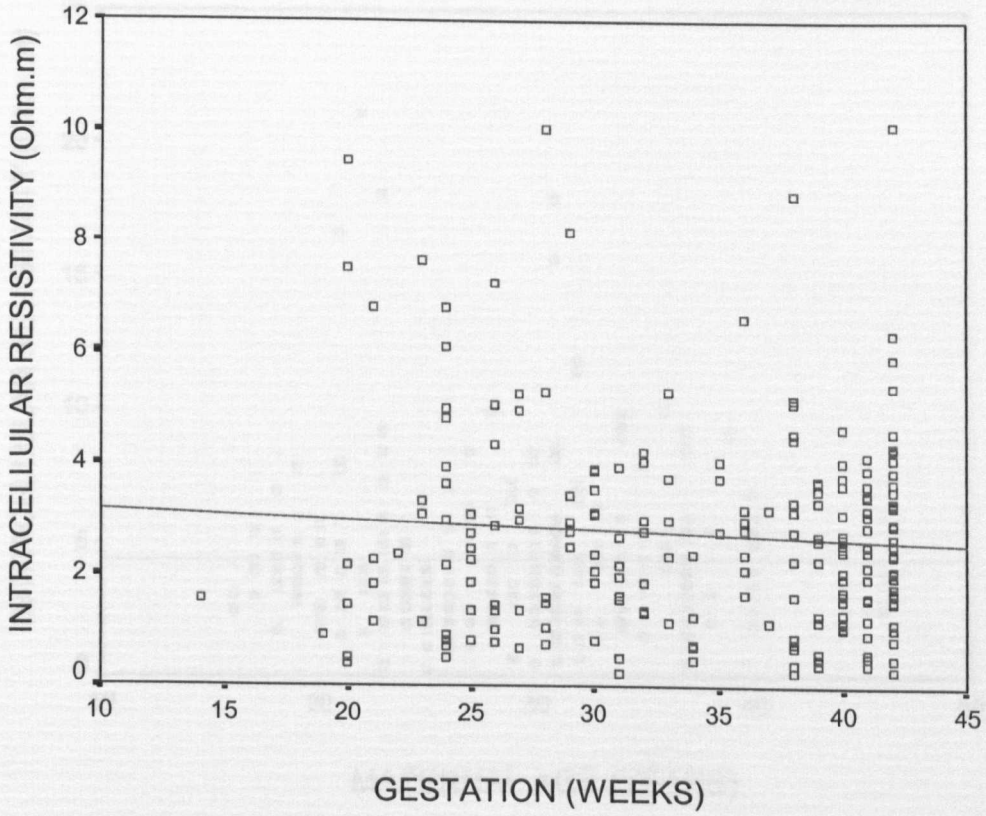

Figure 3.8 A comparison of intracellular resistivity versus gestational age using the 8mm probe. The best fit line is superimposed.

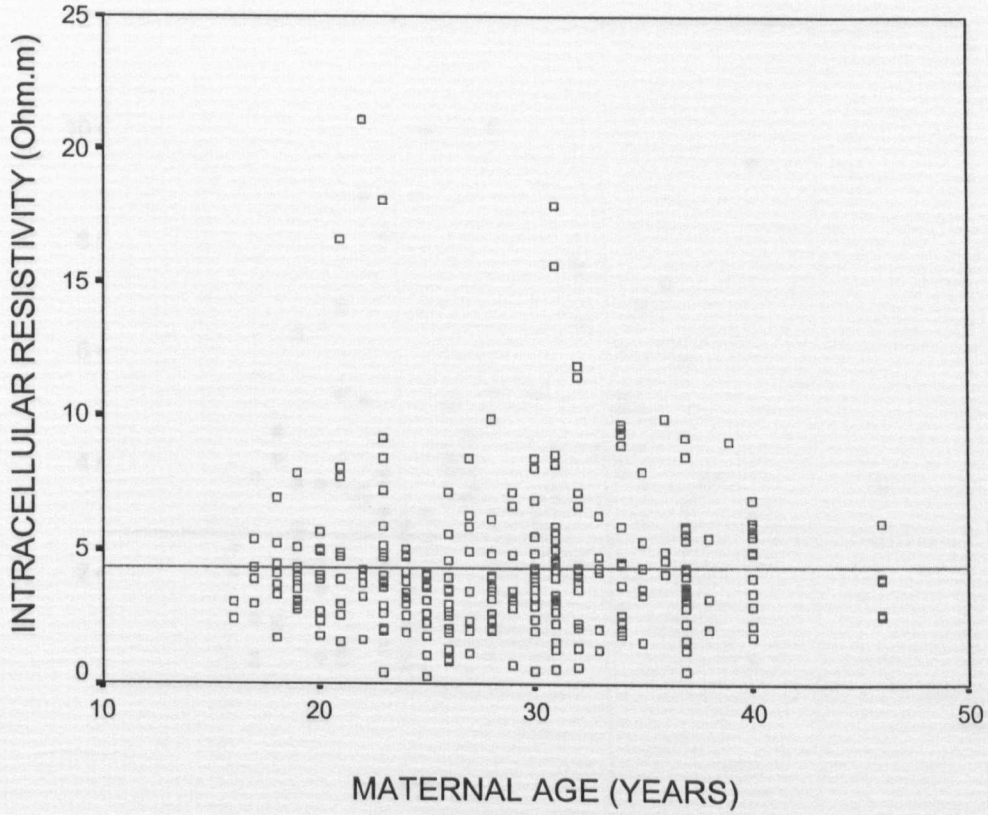

Figure 3.9 A comparison of intracellular resistivity versus maternal age using the 5.5mm probe. The best fit line is superimposed.

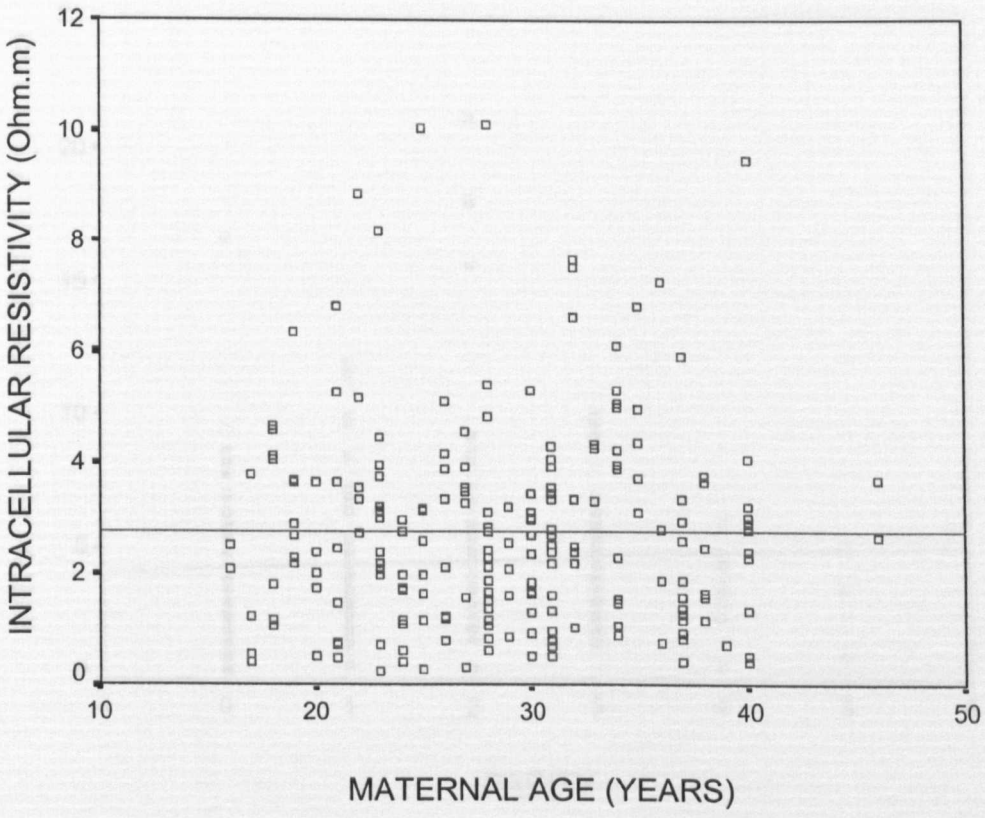

Figure 3.10 A comparison of intracellular resistivity versus maternal age using the 8mm probe. The best fit line is superimposed.

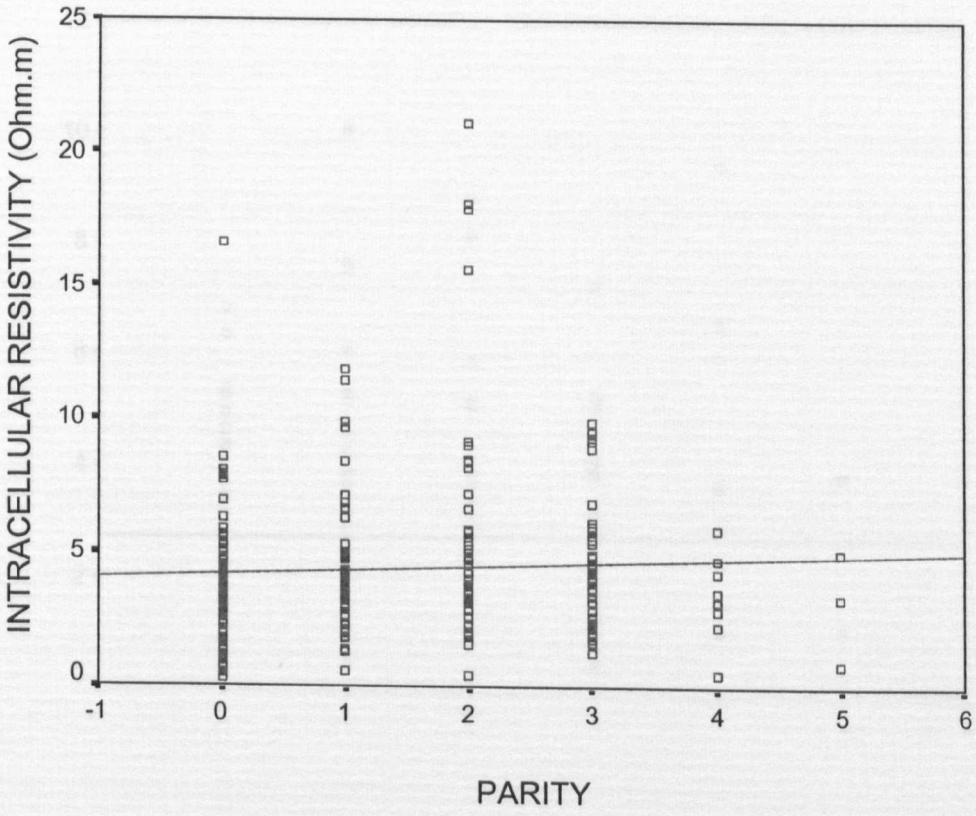

Figure 3.11 A comparison of intracellular resistivity versus parity using the 5.5mm probe. The best fit line is superimposed.

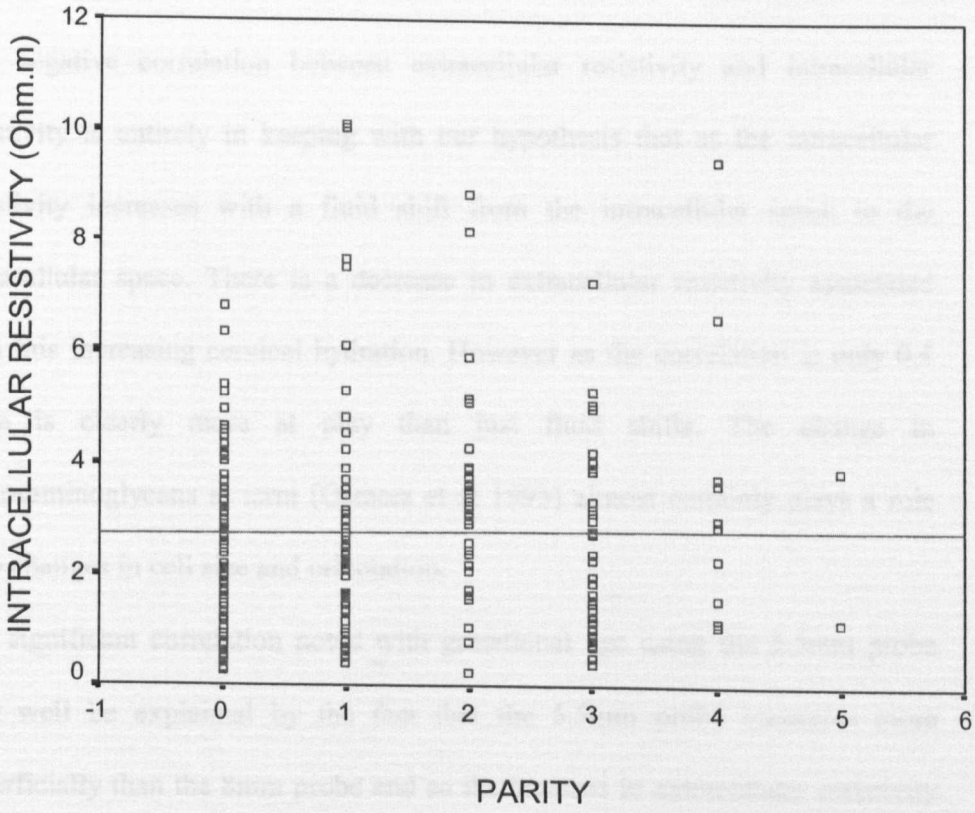

Figure 3.12 A comparison of intracellular resistivity versus parity using the 8mm probe. The best fit line is superimposed.

3.4 DISCUSSION

The negative correlation between extracellular resistivity and intracellular resistivity is entirely in keeping with our hypothesis that as the intracellular resistivity increases with a fluid shift from the intracellular space to the extracellular space. There is a decrease in extracellular resistivity associated with this increasing cervical hydration. However as the correlation is only 0.4 there is clearly more at play than just fluid shifts. The change in glycosaminoglycans at term (Osmers et al 1993) almost certainly plays a role with changes in cell size and orientation.

The significant correlation noted with gestational age using the 5.5mm probe may well be explained by the fact that the 5.5mm probe measures more superficially than the 8mm probe and so the increase in extracellular resistivity can be explained by the fact that we may not be measuring the process of effacement at the appropriate level. To clarify this finding we are currently using a distant electrode whilst measuring the electrical impedance measurements in order to characterise the ripening cervix at a deeper level.

Interestingly there were no significant correlations seen between resistivity readings and both parity and maternal age, suggesting that the process of cervical ripening is similar in both primiparous and multiparous patients.

The positive correlation between maternal age and parity is entirely to be expected.

3.5 SUMMARY

This study suggests that maternal age, and parity are not confounding variables in our studies. Gestation age is more difficult to assess as the majority of our patients are of an advanced gestation. Further longitudinal work will be required to clarify the role of gestational age.

CHAPTER 4 THE COMPARISON OF ELECTRICAL IMPEDANCE MEASUREMENTS IN THE PREGNANT AND NON-PREGNANT CERVIX

4.1 AIM OF THE STUDY

To assess the effect of pregnancy on electrical impedance measurements of the cervix, by comparing two groups comprising of non-pregnant and pregnant women.

4.2 METHODS

Transfer impedance measurements were made at a frequency of 4.8kHz using a 5.5mm diameter pencil probe, with four gold electrodes mounted flush with the face of the probe. The probe is placed on the surface of the cervix and does not enter the substance of the cervical tissue. A current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential was measured between the remaining pair (as described in chapter 3).

A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the average calculated.

Both sets of data were collected on identical instruments calibrated by the Department of Medical Physics in University of Sheffield. The calibration was made before each set of results by placing the probe in saline solutions with a range of concentrations and hence electrical resisitvities. The in-vivo results are thus presented in units of Ohm metres (Ωm).

Ethical approval was granted for this study and all patients gave informed written consent.

Measurements were made in 78 pregnant women in the delivery suite at the time of induction of labour prior to any intervention. The mean Bishop score was 3.25 (range 0-10). The probe was placed anteriorly on the cervix and a minimum of 4 recordings were made.

Measurements were made in 195 non-pregnant women in the colposcopy clinic. The probe was placed in 8 positions (medial and lateral reading at 3, 6, 9, and 12 o clock) on the cervix. In all cases two separate sets of data were recorded. Only patients in the reproductive age group (age 16-44 years) were included in the analysis.

4.3 RESULTS

The values for the measured electrical impedance parameters in the non pregnant and pregnant patients are shown in tables 4.1 and 4.2 .

An average value for resisitivity was obtained by taking a mean of all recordings made in each patient. The data was analysed using a non-parametric test (Mann-Whitney U), with a median value of 20.52 (interquartile range 13.38) and 10.01 (interquartile range 4.28) for the non-pregnant and pregnant patients respectively. A significant difference was noted in resistivity for pregnant and non-pregnant patients ($p < 0.001$).

The boxplots indicate differences in the median resistivity for pregnant and non-pregnant women (fig.4.1).

PARAMETER	R	S	R/S	LnR/S	Fc
MEAN	18.85	3.09	16.5	2.19	12.64
STANDARD DEVIATION	8.52	6.6	22.28	1.13	9.3
95% CONFIDENCE INTERVAL Lower	17.65	2.16	13.36	2.03	11.32
95% CONFIDENCE INTERVAL Upper	20.05	4.02	19.65	2.35	13.95
MEDIAN	20.52	2.07	9.78	2.28	11.55
MINIMUM VALUE	1.56	0.04	.39	-.94	.2
MAXIMUM VALUE	30	76.38	100.48	4.61	63.84
INTERQUARTILE RANGE	13.38	2.39	12.85	1.36	10.53

Table 4.1 Tissue measurements non-pregnant patients. Statistical data for the non-pregnant patients. R and S are measured in Ωm, and Fc is measured in kHz.

PARAMETER	R	S	R/S	LnR/S	Fc
MEAN	10.01	4.0	3.43	0.93	25.76
STANDARD DEVIATION	4.28	2.0	3.06	0.8	36.41
95% CONFIDENCE INTERVAL Lower	9.04	3.55	2.74	.75	17.55
95% CONFIDENCE INTERVAL Upper	10.97	4.45	4.11	1.11	33.97
MEDIAN	10.23	3.96	2.5	0.92	15.39
MINIMUM VALUE	1.82	0.4	0.15	-1.88	1.69
MAXIMUM VALUE	24.07	15.84	20.7	3.03	216
INTERQUARTILE RANGE	6.02	1.99	2.52	0.94	12.66

Table 4.2 Tissue measurements pregnant patients. Statistical data for the pregnant patients. R and S are measured in Ωm, and Fc is measured in kHz.

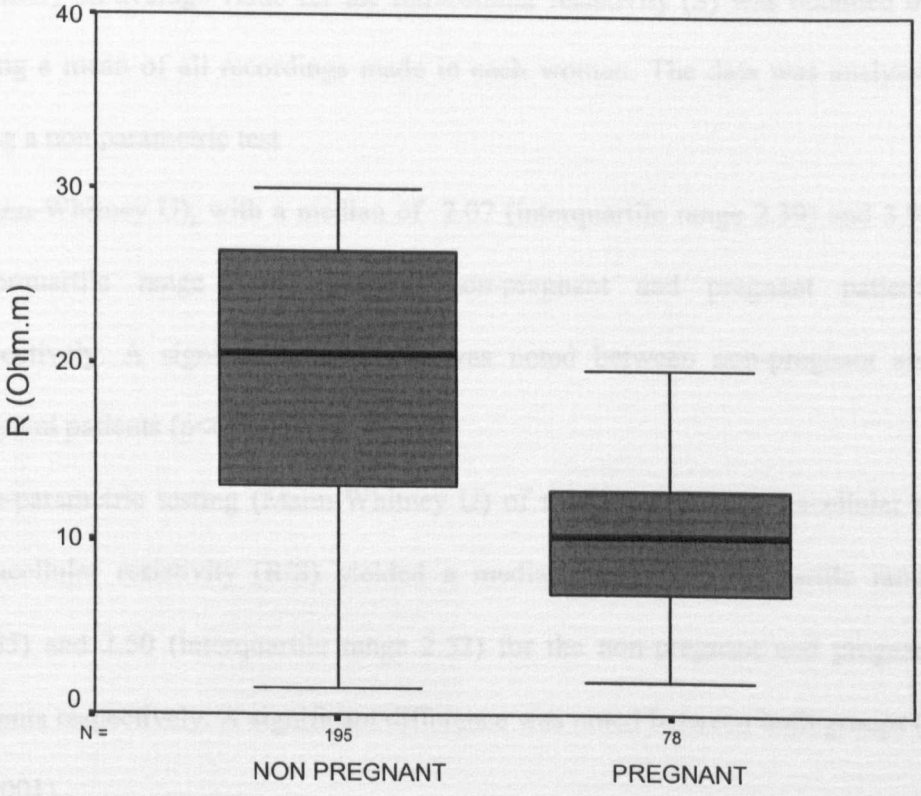

Figure 4.1 Resistivity measurements in the non-pregnant and pregnant cervix. The median, interquartile range and the absolute range is shown.

Similarly an average value for the intracellular resistivity (S) was obtained by taking a mean of all recordings made in each woman. The data was analysed using a non parametric test

(Mann-Whitney U), with a median of 2.07 (interquartile range 2.39) and 3.96 (interquartile range 1.99) for the non-pregnant and pregnant patients respectively. A significant difference was noted between non-pregnant and pregnant patients ($p<0.001$).

Non-parametric testing (Mann-Whitney U) of the ratio of the extracellular to intracellular resistivity (R/S) yielded a median of 9.78 (interquartile range 12.85) and 2.50 (interquartile range 2.52) for the non-pregnant and pregnant patients respectively. A significant difference was noted between both groups ($p < 0.001$).

There was a significant difference ($p < 0.001$) between both groups on analysis of the characterisitc frequency (Fc), with a median of 11.55 (interquartile range 10.53) and 15.39 (interquartile range 12.66) for the non-pregnant and pregnant patients respectively.

The box plots indicate differences in the intracellular resistivity for the pregnant and non pregnant patients (fig.4.2).

Figures 4.3 and 4.4 show the mean +/- 2 standard errors of the mean for the extracellular resistivity (R) and the intracellular resisitivity (S) respectively.

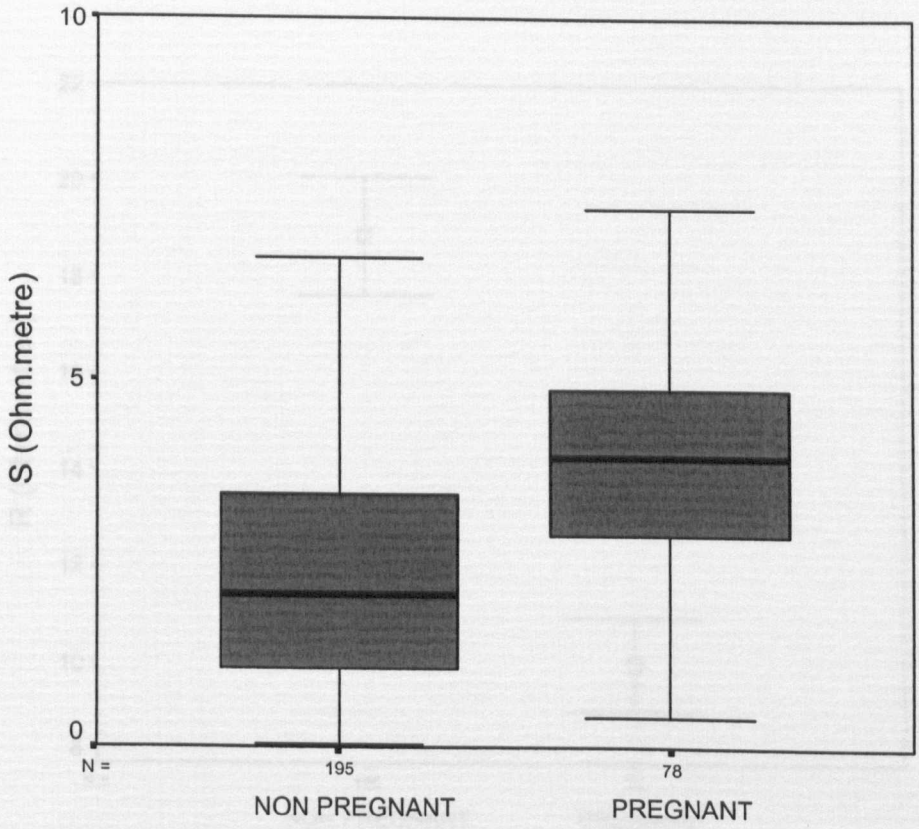

Figure 4.2 Intracellular resistivity measurements in the non-pregnant and pregnant cervix. The median, interquartile range and the absolute range is shown.

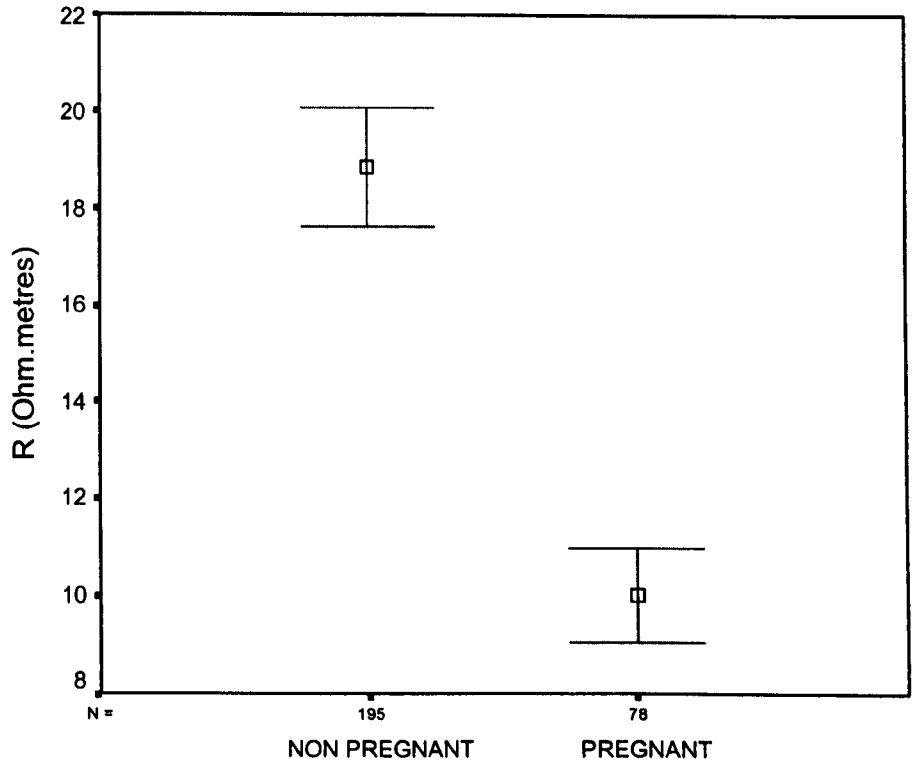

Figure 4.3 The mean +/- 2 standard errors of the mean extracellular resistivity (R) for the non-pregnant and pregnant cervix is shown.

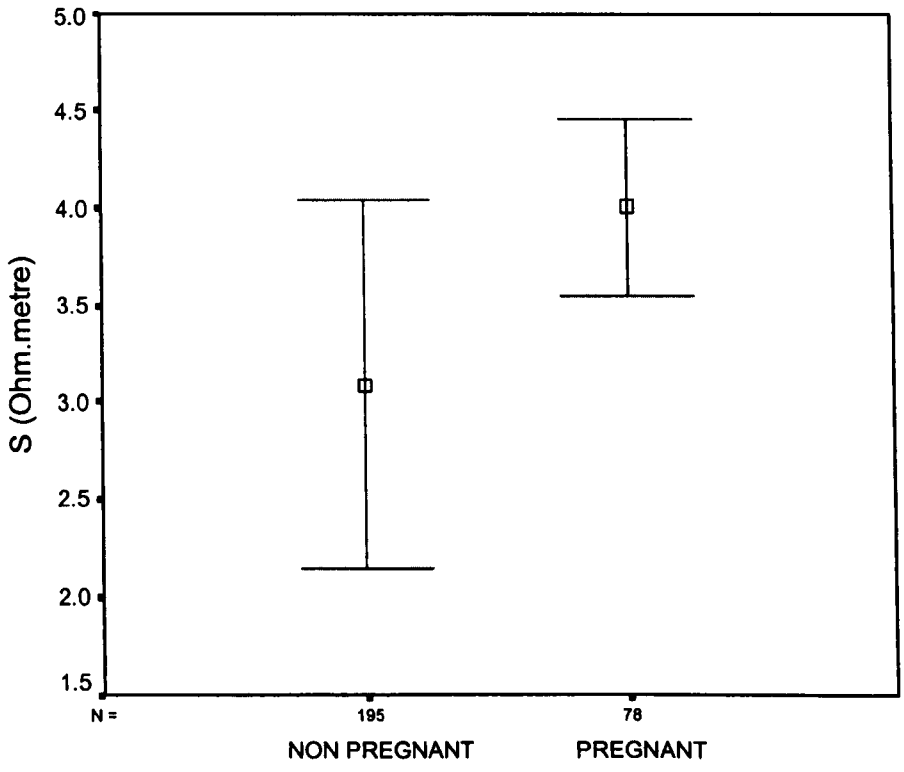

Figure 4.4 The mean +/- 2 standard errors of the mean intracellular resistivity (S) for the non- pregnant and pregnant cervix is shown.

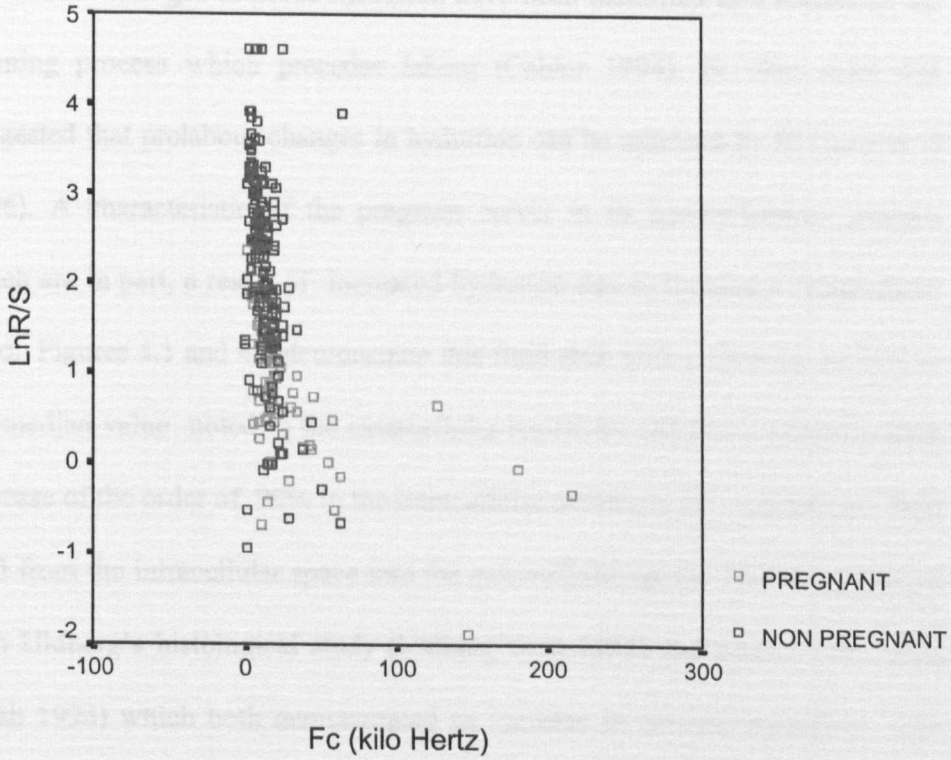

Figure 4.5 A plot of the natural log of the R/S ratio against the characteristic frequency (Fc) for the non-pregnant and pregnant cervix.

4.4 DISCUSSION

Cumulative changes in tissue hydration have been identified as a feature of the ripening process which precedes labour (Calder 1994). In vitro work has suggested that prelabour changes in hydration can be assessed by EI (Avis et al 1996). A characteristic of the pregnant cervix is its biomechanical changes which are in part, a result of increased hydration due to increased extracellular fluid. Figures 4.1 and 4.2 demonstrate this fluid shift with a decrease of 49% in the median value noted in the extracellular resistivity (R) and a corresponding increase of the order of 90% in the intracellular resistivity (S), indicating a fluid shift from the intracellular space into the extracellular space. This is consisitent with Uldberg's histological study (Uldberg et al 1983) and Oláh's MRI work (Oláh 1994) which both demonstrated an increase in cervical hydration with increasing gestation.

Analysis of the resisitvity values using mean and standard errors of the mean was undertaken as all the readings were the mean of 4 points of the cervix which were also the mean of 100 readings means. The results are expressed in figures 4.3 and 4.4 and show statistically significant separation between the pregnant and non-pregnant cervix ($p< 0.01$) for the extracellular resisitivity and a non-significant t difference ($p< 0.08$) for the intracellular resistivity using the independent t test.

Plotting a natural log ratio of the extracellular resisitvity (R) over the intracellular resistivity (S) against the characteristic frequency (Fc) it is possible to differentiate between the pregnant and non-pregnant cervix (Fig. 4.5).

This study demonstrates the ability of electrical impedance measurements to discriminate between the pregnant and the non-pregnant cervix. This difference seen in pregnancy is consistent with a decrease in extracellular resistivity which could be expected with an increase in tissue hydration and a rise in intracellular resisitivity consistent with a fluid shift from the intracellular to the extracellular space.

However this may not be the only explanation. The changes could be related to changes in electrical activity or connections between cervical muscle fibres, or to the major modification in connective tissue composition or indeed to changes in cell orientation which are all seen towards the end of pregnancy.

The magnitude of the difference found in resisitvity of the normal and pregnant cervix was 49%. This change could be the result of changes in both the structure and composition of the cervical tissue. Brown et al (2000) found changes of a similar magnitude in the pre-cancerous cervix and ascribed these to differences in tissue structure. Detailed modelling of the likely effect of structural changes in cervical tissue during pregnancy is needed in order to give a definitive explanation of our measurements.

4.5 SUMMARY

In this study of pregnant and non-pregnant women a statistically significant difference in the electrical resistance (resistivity) both at extracellular and intracellular levels has been demonstrated. The changes demonstrated are in accordance with the physiological changes of the pregnant cervix which have been reported both at a histological and biochemical level (see Chapter 1).

4.6 CONCLUSION

Electrical impedance measurements demonstrate a statistically significant difference between the non-pregnant and pregnant cervix.

CHAPTER 5 ELECTRICAL IMPEDANCE MEASUREMENTS - AN OBJECTIVE MEASURE OF THE CERVIX AT THE TIME OF INDUCTION OF LABOUR STUDY

5.1 INTRODUCTION

Induction of labour is an obstetric procedure designed to pre-empt the natural process of labour by initiating its onset artificially before this occurs spontaneously. The clinical procedures which have been used by obstetricians in order to induce labour have been many and varied and are by no means universally accepted. The longest established procedure is that of surgical amniotomy, which was introduced by Thomas Denman in the mid-18th century with the aim of preventing the complications of cephalopelvic disproportion by induction of labour prematurely in order to deliver a smaller baby. In Denman's era the unpredictability of labour onset post surgical amniotomy was a source of concern. The greater the interval to labour, the greater was the risk of sepsis intervening often with fatal consequence to both mother and baby.

In view of the risks of amniotomy in the past clinicians sought to avoid this procedure where possible. Tarnier in Paris in 1862 (Speert 1958) mechanically dilated the cervix by placing a soft rubber bag the size of a hen's egg through the cervix on the end of a male catheter. Champetier de Ribes modified this approach by devising a conical-shaped silk device which was covered in rubber and was introduced through the cervix with a forceps prior to dilating it with fluid. More recently dilatation and effacement of the cervix has been achieved by the introduction, under aseptic technique, of a catheter with an inflatable balloon through the cervix. The catheter is introduced just above the internal os and the balloon distended with 30-50 millilitres of sterile isotonic saline. The catheter is spiggoted and either left free of connected to a weight to provide

traction against the internal os to procure effacement and dilatation (Embry and Mollison 1967, Lewis 1983). Once adequate dilatation has been achieved the catheter will pass through the cervix. Thereafter induction can be procured by surgical amniotomy. Active research continues in this area particularly in the developing world where sepsis is still a real risk to mother and baby and where cost often prohibits the widespread use of hormonal methods for induction of labour (Jasper et al 2000, Suri et al 2000). Other mechanical methods such as the use of bougies (Manabe et al 1982) and hygroscopic tents (Lackritz et al 1979, MacPherson 1984) have undergone evaluation but have been largely superseded by hormonal methods of induction.

The hormone which has been most widely used for induction of labour is oxytocin. Until the availability of a reliable synthetic form (Boissonas et al 1955), the use of oxytocin was fraught with difficulty due to problems with impurity and varying potency. Prior to 1968 the buccal route was the favoured route of administration of oxytocin. This was superseded by the intravenous route which was shown to be more satisfactory in terms of fine control when oxytocin was titrated against uterine response following amniotomy (Turnbull and Anderson 1968). This principle of amniotomy and oxytocin infusion has been applied almost universally in maternity hospitals. However the generation of uterine contractility with oxytocin is only part of the picture. The role of the cervix in induction of labour has gained greater prominence since the introduction of prostaglandin's in clinical practice. The degree of cervical ripeness can be assessed using a scoring system such as that described by Bishop (1964), that the presence of a ripe cervix heralded the onset of labour

within a few days whereas the presence of an unripe cervix heralded a delay in labour onset by a number of weeks. This was independent of gestational age. Bishop only applied his score to multiparous patients. Similar findings apply to primparous patients. It is clear that while amniotomy followed by the intravenous titration of oxytocin is an efficient means of induction of labour, its success declines in parallel with the degree of cervical ripeness (Calder 1977). Therefore priming an unripe cervix with prostaglandin (particularly PGE_2) prior to induction with amniotomy and oxytocin provides the best chance of successful induction of labour. The role of prostaglandin's in cervical ripening has been discussed in chapter 1. Clinically there is a choice of three different routes for local administration. The extra-amniotic route (Calder et al 1977) is probably the most effective but less acceptable to the mothers concerned. A dose of 300-500μg of prostaglandin E_2 gel is generally sufficient. Most mothers find the vaginal route more acceptable, but higher doses of prostaglandin are required, up to 2mg of prostaglandin E_2 is effective in the majority of cases (McKenzie and Embrey 1977). This route may be less successful in cases with an unripe cervix. The third option is more popular in continental Europe and involves the intracervical administration of the prostaglandin (Ulmsten et al 1979).

In Hull Maternity Hospital prostaglandin pessaries are used for cervical priming. The position, effacement and dilatation of the cervix is determined prior to insertion of the prostaglandin pessary in the posterior vaginal fornix. All women with pregnancies complicated by intra-uterine growth restriction, evidence of placental insufficiency, or who are asthmatic are given an initial dose of 3mg

prostaglandin pessary (PGE_2 3mg). These patients are induced in the mornings. The prostaglandin is repeated 6 hours later if the cervix is not suitable for amniotomy. The patients are then left overnight and reassessed in the morning primigravida patients are allowed up to a further 2 doses of PGE_2 3mg prior to amniotomy. Multigravida receive a third dose of prostaglandin following consultation with the consultant or the senior registrar. Primigravida patients considered low-risk using this protocol may have an initial dose of PGE_2 6mg if unfavourable followed by up to 2 further 3mg PGE_2 doses at 6 hourly intervals if required (Appendix 4).

5.2 MEASUREMENT OF ELECTRICAL IMPEDANCE PARAMETERS PRIOR TO ANY INTERVENTION AT THE TIME OF INDUCTION OF LABOUR

5.2.1 Patients and methods

96 women underwent assessment, at the time of induction of labour, prior to any intervention (before digital cervical assessment, before artificial rupture of the membranes and before insertion of prostaglandin pessary) using the 5mm tetrapolar probe, and 79 women were assessed prior to any intervention using the 8mm probe. The women then had a digital vaginal examination and the Bishop score was determined. Those with a Bishop score of ≤ 4 were deemed unfavourable while those with a Bishop score of ≥ 5 were deemed favourable. Transfer impedance measurements were made at a frequency of 4.8kHz using the 5.5mm and 8mm diameter pencil probes, each with four gold electrodes mounted flush with the face of the probe.

In all cases the probe was placed on the surface of the cervix and did not enter the substance of the cervical tissue. A current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential was measured between the remaining pair.

The unfavourable group were given a prostaglandin pessary, while the favourable group had an artificial rupture of membranes.

5.2.2 Results

The values for the measured electrical impedance parameters are shown in table 5.1 for the 5.5mm probe and table 5.2 for the 8mm probe.

A separate average value for extracellular resistivity (R) for each probe was obtained by taking a mean of all recordings in each woman. As the data assumed a normal distribution statistical analysis was performed using the independent sample t test. The mean value (95% confidence interval) using the 5.5mm probe was 9.90 (8.86- 11.18) Ωm for the unfavourable group and 10.23 (8.86- 11.59) Ωm for the favourable group. Corresponding values using the 8mm probe were 6.86 (5.41-8.31) Ωm for the unfavourable group and 5.34 (4.59-6.09) Ωm for the favourable group. No statistically significant difference was noted when assessing for extracellular resistivity in the unfavourable and favourable group with either probe. However a p value (0.076) approaching statistical significance was seen with the 8mm probe.

The boxplots indicate differences in the median extracellular resistivity (R) for the unfavourable and favourable cervices using the 5.5mm (figure 5.1) and 8mm (figure 5.2) probes respectively. Figures 5.3 and 5.4 show the mean +/- 2 standard errors of the mean for R using the 5mm and 8mm probes respectively.

Similarly an average value for intracellular resistivity (S) was obtained by taking a mean of all recordings made with both probes in each woman. The mean (95% confidence interval) for the 5mm probe was 3.76 (3.31- 4.21) for the unfavourable group and 3.67 (2.99- 4.35) for the favourable group (figure 5.5). For the 8mm probe the mean was 2.55 (2.05- 3.04) and 2.96 (2.33 - 3.59) for the unfavourable and favourable groups respectively (Figure 5.6). Neither group demonstrated a statistically significent result using the independent t test.

Analysing the mean extracellular (R) to intracellular (S) ratio, the characteristic frequency (Fc) and a natural logarithmic transformation of the R/S ratio failed to demonstrate any difference between the unfavourable and favourable groups with either probe.

Figures 5.7 and 5.8 show plots of the natural logarithmic transformation of the R/S ratio against the Fc. The natural logarithmic transformation was employed to clarify if differences really existed in the R/S ratio between the favourable and the unfavourable cases.

PARAMETER		R	S	R/S	LnR/S	Fc
MEAN	Unfavourable	9.90	3.76	4.22	0.93	22.80
	Favourable	10.23	3.67	4.33	0.91	31.87
STANDARD DEVIATION						
	Unfavourable	4.55	1.61	5.42	0.79	25.21
	Favourable	4.54	2.28	5.35	0.88	46.12
95% CONFIDENCE INTERVAL Lower						
	Unfavourable	8.62	3.31	2.70	0.71	15.71
	Favourable	8.86	2.99	2.72	0.65	18.01
95% CONFIDENCE INTERVAL Upper						
	Unfavourable	11.18	4.21	5.75	1.15	29.89
	Favourable	11.59	4.35	5.94	1.17	45.72
MEDIAN	Unfavourable	10.23	3.85	2.32	0.84	15.53
	Favourable	10.23	3.51	3.14	1.07	15.45
MINIMUM VALUE	Unfavourable	1.82	0.50	0.45	-0.80	4.89
	Favourable	2.38	0.30	0.15	-1.88	1.69
MAXIMUM VALUE	Unfavourable	22.83	8.37	26.09	3.30	162.23
	Favourable	24.07	15.58	33.03	2.82	216.00
INTERQUARTILE RANGE						
	Unfavourable	7.03	1.71	2.87	1.99	16.36
	Favourable	6.51	1.80	3.08	1.15	17.97

Table 5.1 Tissue measurements in women at induction of labour using the 5.5mm probe. R and S are measured in Ωm, and Fc is measured in kHz.

PARAMETER		R	S	R/S	LnR/S	Fc
MEAN	Unfavourable	6.85	2.55	4.20	0.83	29.46
	Favourable	5.34	2.96	2.79	0.52	30.40
STANDARD DEVIATION						
	Unfavourable	4.35	1.48	4.46	1.11	42.05
	Favourable	2.07	1.75	4.63	0.95	47.97
95% CONFIDENCE INTERVAL Lower						
	Unfavourable	5.41	2.05	2.71	0.46	15.43
	Favourable	4.59	2.33	1.12	0.18	13.11
95% CONFIDENCE INTERVAL Upper						
	Unfavourable	8.31	3.04	5.69	1.20	43.48
	Favourable	6.09	3.59	4.46	0.86	47.70
MEDIAN	Unfavourable	5.37	2.44	2.20	0.78	15.80
	Favourable	5.34	2.90	1.52	0.46	16.01
MINIMUM VALUE	Unfavourable	2.17	0.26	0.34	-1.09	1.72
	Favourable	2.27	0.31	0.41	-0.92	1.57
MAXIMUM VALUE	Unfavourable	20.66	6.34	16.50	2.80	188.74
	Favourable	11.15	10.09	26.44	3.27	242.48
INTERQUARTILE RANGE						
	Unfavourable	5.16	2.39	6.18	1.99	26.02
	Favourable	3.05	1.54	1.57	1.15	16.86

Table 5.2 Tissue measurements in women at induction of labour using the 8mm probe. R and S are measured in Ωm, and Fc is measured in kHz.

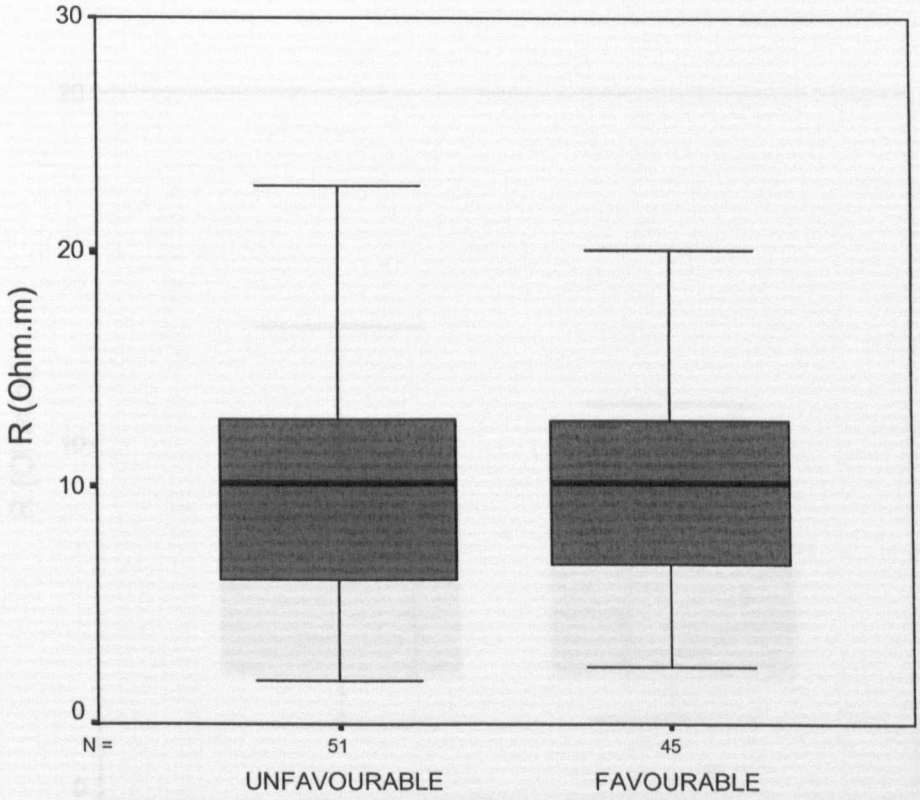

Figure 5.1 Extracellular resistivity (R) measurements using the 5.5mm probe at the time of induction of labour. The median, interquartile range and the absolute range is shown. The two outlying values are excluded.

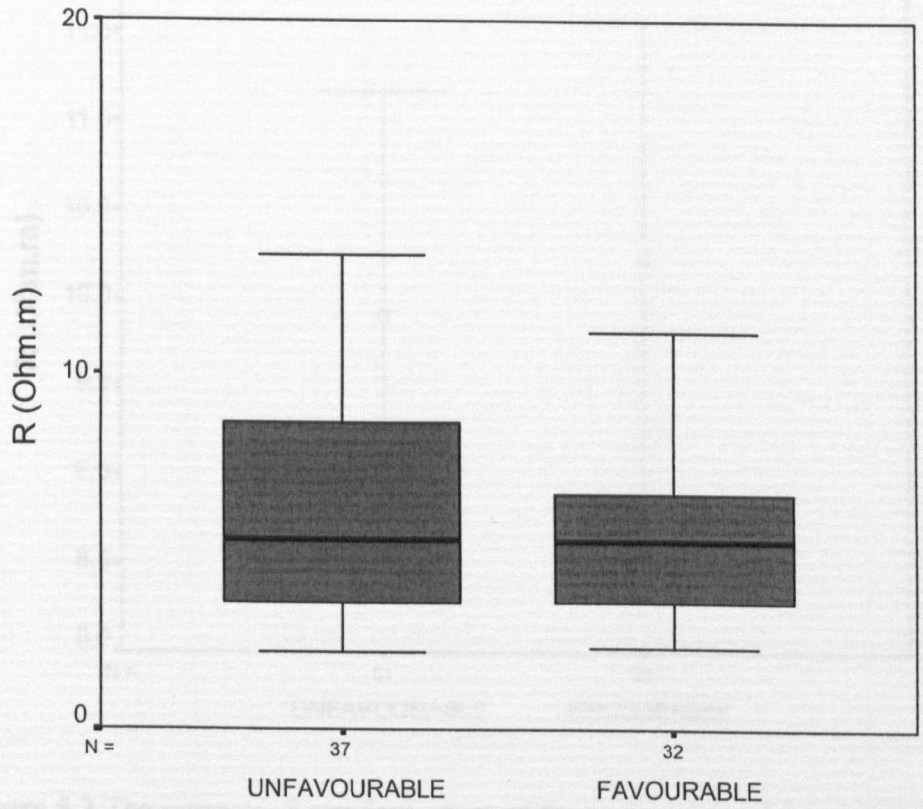

Figure 5.2 Extracellular resistivity (R) measurements using the 8mm probe at the time of induction of labour. The median, interquartile range and the absolute range is shown. The two outlying values are excluded.

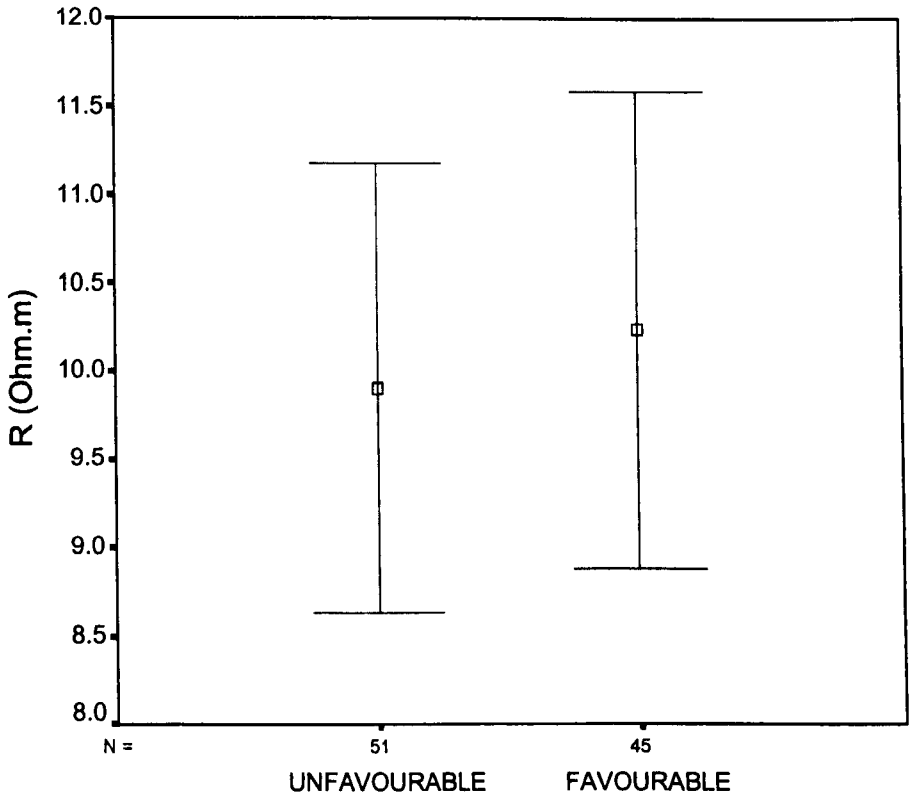

Figure 5.3 The mean +/- 2 standard errors of the mean extracellular resistivity (R) using the 5.5mm probe for the unfavourable and favourable cervices at the time of induction of labour.

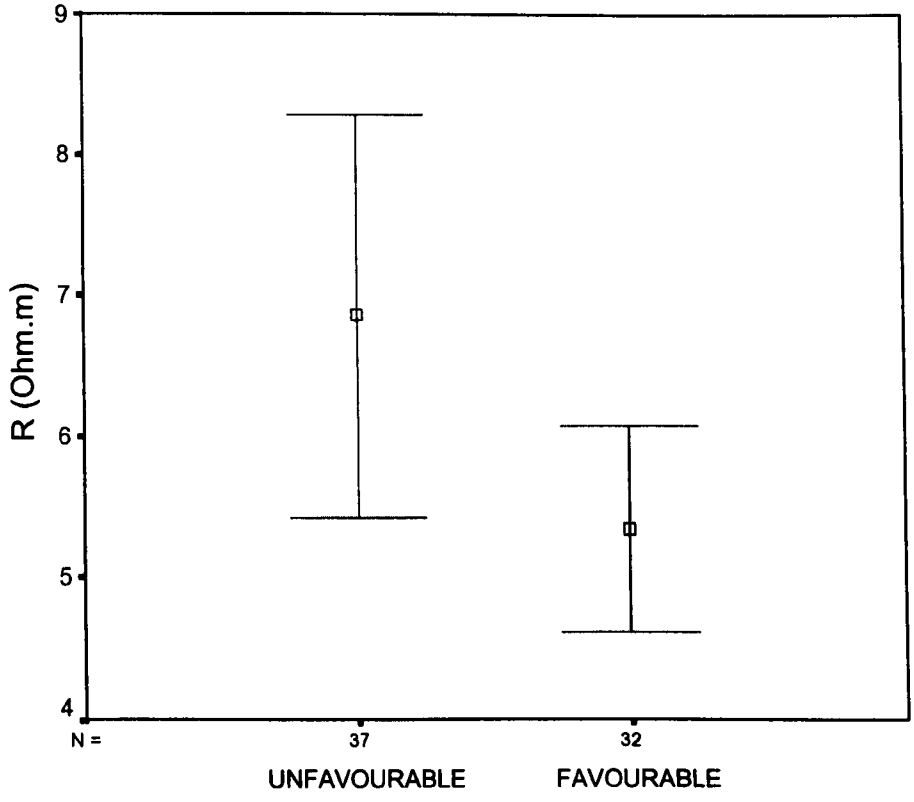

Figure 5.4 The mean +/- 2 standard errors of the mean extracellular resistivity (R) using the 8mm probe for the unfavourable and favourable cervices at the time of induction of labour.

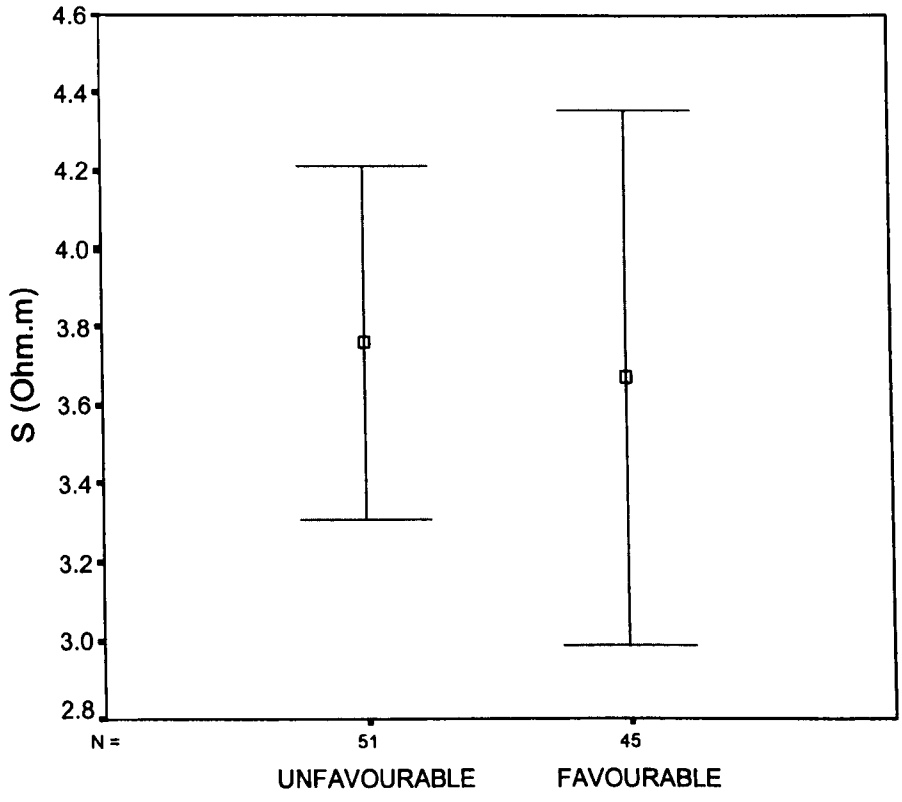

Figure 5.5 The mean +/- 2 standard errors of the mean intracellular resisitvity (S) using the 5.5mm probe at the time of induction of labour for the unfavourable and favourable cervices.

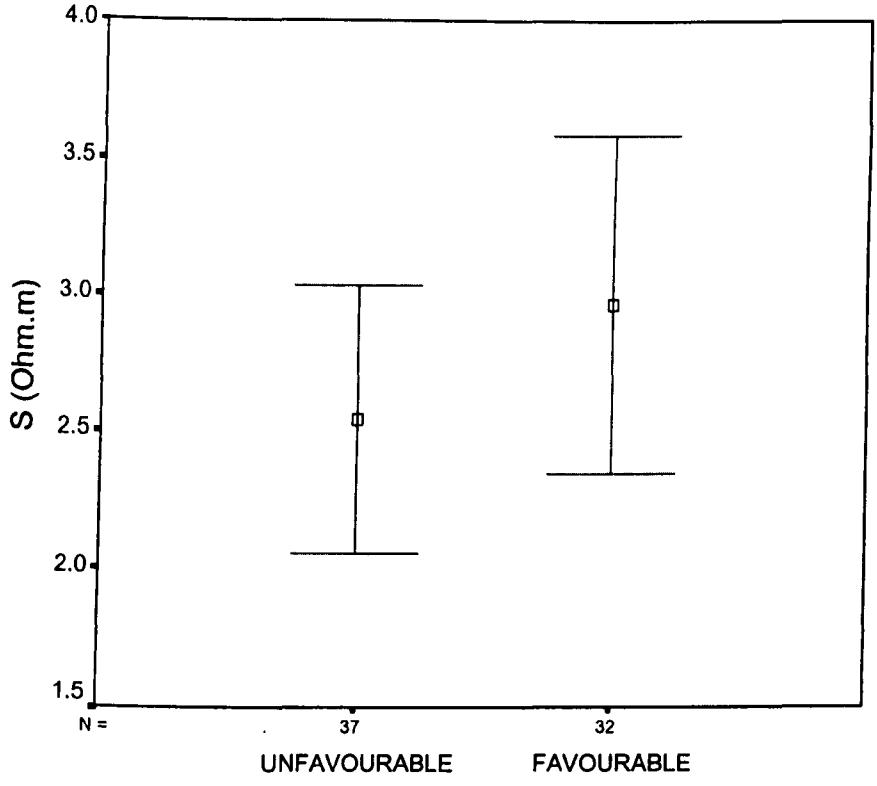

Figure 5.6 The mean +/- 2 standard errors of the mean intracellular resisitvity (S) using the 8mm probe at the time of induction of labour for the unfavourable and favourable cervices.

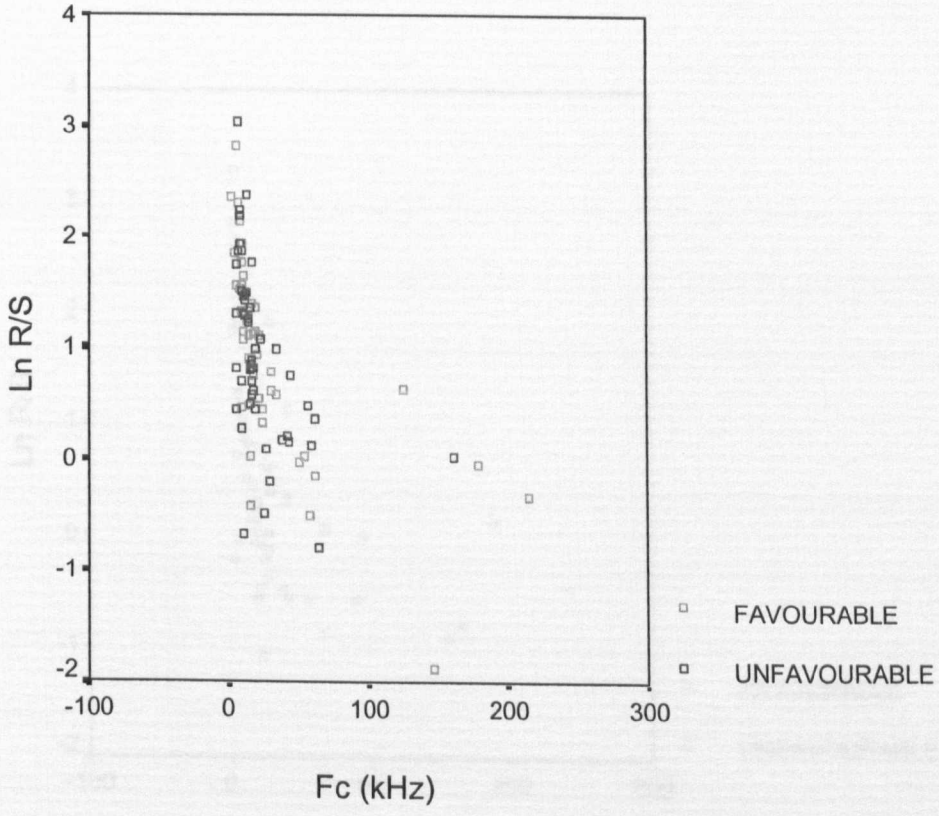

Figure 5.7 A plot of the natural log of the extracellular to intracellular (R/S) ratio against the characteristic frequency (Fc) using the 5.5mm probe for unfavourable and favourable cervices at induction of labour.

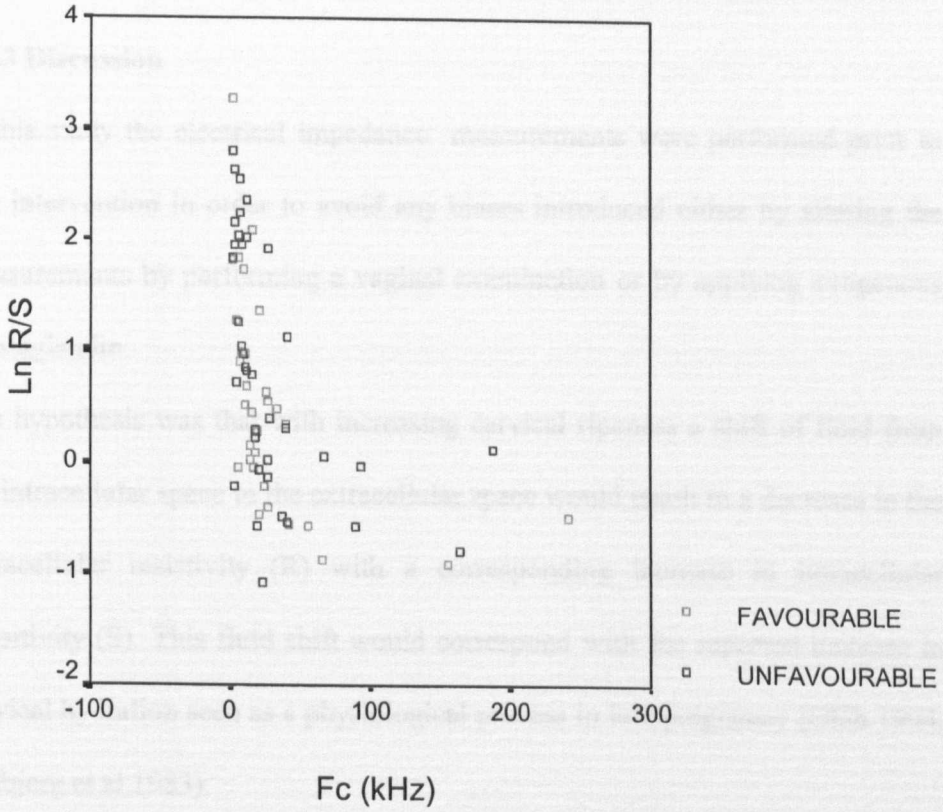

Figure 5.8 A plot of the natural log of the extracellular to intracellular (R/S) ratio against the characteristic frequency (Fc) using the 8mm probe for unfavourable and favourable cervices at induction of labour.

5.2.3 Discussion

In this study the electrical impedance measurements were performed prior to any intervention in order to avoid any biases introduced either by altering the measurements by performing a vaginal examination or by applying exogenous prostaglandin.

The hypothesis was that with increasing cervical ripeness a shift of fluid from the intracellular space to the extracellular space would result in a decrease in the extracellular resistivity (R) with a corresponding increase in intracellular resisitivity (S). This fluid shift would correspond with the reported increase in cervical hydration seen as a physiological process in late pregnancy (Oláh 1994, Uldbjerg et al 1983).

Using the 5.5mm probe no differences between the unfavourable and favourable groups were demonstrated, regardless of the electrical impedance measurement employed. However using the 8mm probe it was possible to demonstrate a decrease in extracellular resisitivity with a marginal increase in intracellular resisitivity. These changes between the unfavourable and favourable groups did not reach statisitical significance. The trends in the electrical impedance measurements were in the direction predicted by our hypothesis.

It is known that the depth of penetration of the probe is inversely related to the probe diameter and so the 8mm probe would be expected to measure the cervix at a deeper level than the 5.5mm probe. If effacement begins at the internal cervical os then it is conceptually sound to expect to see changes in the

electrical impedance measurements sooner using the 8mm probe than when using the 5mm probe. This is in accordance with findings as outlined above.

This study is limited by the fact that none of these patients had electrical impedance readings taken prior to admission for induction of labour and so it was not possible to relate the readings at induction of labour to any other reading at another time in pregnancy for that patient.

Those women omitted from the analysis on the basis of their readings being too low to be reliable were excluded following advice from the medical physicists. The minimum value for resistivity that we agreed to be interpretable was 1.5Ωm. Once the learning curve was achieved in taking the electrical impedance measurements namely after 50 readings then none of the readings were excluded from the analysis.

5.2.4 Summary

Electrical impedance measurements at the time of induction of labour prior to any intervention using the 5.5 mm probe failed to demonstrate any difference between the favourable and unfavourable cervix. However using the 8mm probe there was a trend towards a decrease in extracellular resistivity with a less apparent trend towards an increase in intracellular resistivity. The differences between the probes may well be due to their different depths of penetration of the cervix.

The 8mm probe discriminated better between the favourable and unfavourable cervix. This was probably due to its greater depth of penetration of the cervix. However the differecnces did not reach statistical significance.

5.3 Measurement of electrical impedance parameters pre- and post-intervention at the time of induction of labour.

5.3.1 Patients and methods

In this study 107 women underwent assessment, at the time of induction of labour, using the 5.5mm tetrapolar probe, 8 women were excluded from the analysis as the gain was too low and thus yielded unreliable readings. Of the 99 women included in the analysis 39 had two sets of readings and 6 had three sets of readings, giving 150 sets of readings for analysis in the 5.5mm probe group. A total of 86 women were assessed using the 8mm probe with 12 excluded as the gain was too low thereby yielding unreliable readings. Of the 74 women included for analysis 28 had two sets of readings and 2 had three sets of readings, giving 106 sets of readings for analysis in the 8mm probe group.

In both groups the women initially had a digital vaginal examination and the Bishop score was determined. Those with a Bishop score of ≤ 4 were deemed unfavourable while those with a Bishop score of ≥ 5 were deemed favourable. Transfer impedance measurements were made at a frequency of 4.8kHz using a 5.5mm and 8mm diameter pencil probes, each with four gold electrodes mounted flush with the face of the probe. In both cases the probe was placed on the surface of the cervix and did not enter the substance of the cervical tissue. A current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential was measured between the remaining pair. Prostaglandin was administered as per the hospital policy as outlined above (Appendix 5).

The unfavourable group had a prostaglandin pessary inserted into the posterior vaginal fornix, while the favourable group had an artificial rupture of membranes. If the Bishop score remained ≤ 4 at an assessment 6 hours later then the woman had a further dose of prostaglandin vaginally. Once women had an artificial rupture of membranes then no further electrical impedance measurements were taken.

5.3.2 Results

The values for the measured electrical impedance parameters are shown in table 5.3 for the 5.5mm probe and table 5.4 for the 8mm probe.

A separate average value for extracellular resistivity (R) for each probe was obtained by taking a mean of all recordings in each woman. As the data assumed a normal distribution statistical analysis was performed using the independent sample t test. The mean value (95% confidence interval) using the 5.5mm probe was 10.43 (9.41 - 11.44) Ωm for the unfavourable group and 9.74 (8.55 - 10.93) Ωm for the favourable group. Corresponding values using the 8mm probe were 7.10 (5.90 - 8.30) Ωm for the unfavourable group and 5.64 (4.95 - 6.33) Ωm for the favourable group. A statistically significant difference was noted for extracellular resistivity between the unfavourable and favourable group with the 8mm probe ($p < 0.034$), but not with the 5.5mm probe ($p < 0.384$).

The boxplots indicate differences in the median extracellular resistivity (R) for the unfavourable and favourable cervices using the 5.5mm (figure 5.9) and 8mm (figure 5.10) probes respectively. Figures 5.11 and 5.12 show the mean +/- 2

standard errors of the mean for R using the 5.5mm and 8mm probes respectively.

Similarly an average value for intracellular resistivity (S) was obtained by taking a mean of all recordings made with both probes in each woman. The mean (95% confidence interval) for the 5.5mm probe was 3.64 (3.29 - 4.00) for the unfavourable group and 4.09 (3.27 - 4.90) for the favourable group (figure 5.13). For the 8mm probe the mean was 2.31 (1.91 - 2.71) and 2.96 (2.47 - 3.46) for the unfavourable and favourable groups respectively (figure 5.14). A statistically significant difference was seen between the unfavourable group and the favourable group using the 8mm probe ($p < 0.042$) but no statistical signifiacant difference was seen when the 5mm probe data was similarly analysed.

Analysing the mean extracellular (R) to intracellular (S) ratio, yielded a mean (95% confidence interval) of 4.27 (3.25 - 5.28) for the unfavourable cervices and 4.10 (2.75 - 5.45) for the favourable cervices using the 5.5mm probe and 4.90 (3.50 - 6.31) and 2.88 (1.76 - 4.00) for the unfavourable and favourable cervices respectively using the 8mm probe (figures 5.15 and 5.16). A statistically significent difference was noted between the unfavourable and favourable groups when using the 8mm probe ($p < 0.025$) but not with the 5.5mm probe ($p < .842$).

Figures 5.17 and 5.18 show plots of the narural logarithmic transformation of the R/S ratio against the Fc.

PARAMETER		R	S	R/S	LnR/S	Fc
MEAN	Unfavourable	10.43	3.65	4.27	0.98	29.02
	Favourable	9.74	4.09	4.10	0.81	29.11
STANDARD DEVIATION						
	Unfavourable	4.79	1.66	4.78	0.84	48.23
	Favourable	4.65	3.19	5.26	0.94	42.11
95% CONFIDENCE INTERVAL Lower						
	Unfavourable	9.41	3.30	3.26	0.80	18.86
	Favourable	9.74	3.27	2.75	0.57	18.32
95% CONFIDENCE INTERVAL Upper						
	Unfavourable	11.43	4.00	5.27	1.16	39.18
	Favourable	10.93	4.90	5.45	1.05	39.90
MEDIAN	Unfavourable	10.75	3.67	2.95	0.98	15.53
	Favourable	9.30	3.45	2.71	0.84	16.79
MINIMUM VALUE	Unfavourable	1.82	0.50	0.32	-1.16	1.79
	Favourable	2.38	0.30	0.15	-1.88	1.69
MAXIMUM VALUE	Unfavourable	25.62	8.37	26.09	3.30	300.00
	Favourable	24.07	21.13	33.03	3.03	216.00
INTERQUARTILE RANGE						
	Unfavourable	7.08	1.98	3.42	1.03	18.21
	Favourable	6.51	2.30	2.84	1.01	13.89

Table 5.3 Tissue measurements in women at induction of labour using the 5.5mm probe. R and S are measured in Ωm, and Fc is measured in kHz.

PARAMETER		R	S	R/S	LnR/S	Fc
MEAN	Unfavourable	7.11	2.31	4.90	0.99	24.09
	Favourable	5.65	2.96	2.88	0.53	29.11
STANDARD DEVIATION						
	Unfavourable	4.30	1.43	5.04	1.13	36.63
	Favourable	2.52	1.81	4.08	1.00	43.40
95% CONFIDENCE INTERVAL Lower						
	Unfavourable	5.91	1.91	3.50	0.68	13.89
	Favourable	4.96	2.47	1.77	0.26	17.27
95% CONFIDENCE INTERVAL Upper						
	Unfavourable	8.30	2.71	6.31	1.31	34.28
	Favourable	6.33	2.47	4.00	0.80	40.96
MEDIAN	Unfavourable	5.76	2.18	2.29	0.83	12.04
	Favourable	5.30	2.70	1.58	0.47	16.76
MINIMUM VALUE	Unfavourable	2.17	0.26	0.34	-1.09	1.72
	Favourable	2.27	0.31	0.25	-1.41	1.57
MAXIMUM VALUE	Unfavourable	20.66	6.34	19.80	2.94	188.74
	Favourable	12.45	10.09	26.44	3.27	242.48
INTERQUARTILE RANGE						
	Unfavourable	5.01	2.32	7.39	2.01	21.09
	Favourable	3.34	1.95	2.69	1.50	17.66

Table 5.4 Tissue measurements in women at induction of labour using the 8mm probe. R and S are measured in Ωm, and Fc is measured in kHz.

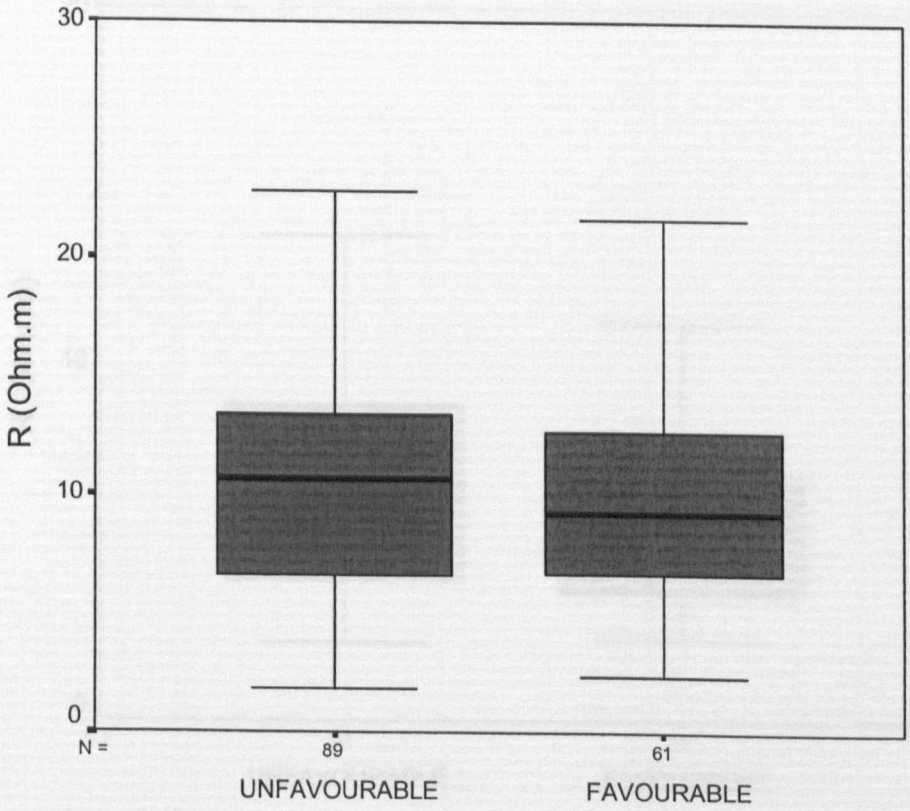

Figure 5.9 Extracellular Resistivity (R) measurements using the 5.5mm probe at the time of induction of labour. The median, interquartile range and the absolute range is shown. The two outlying values are excluded.

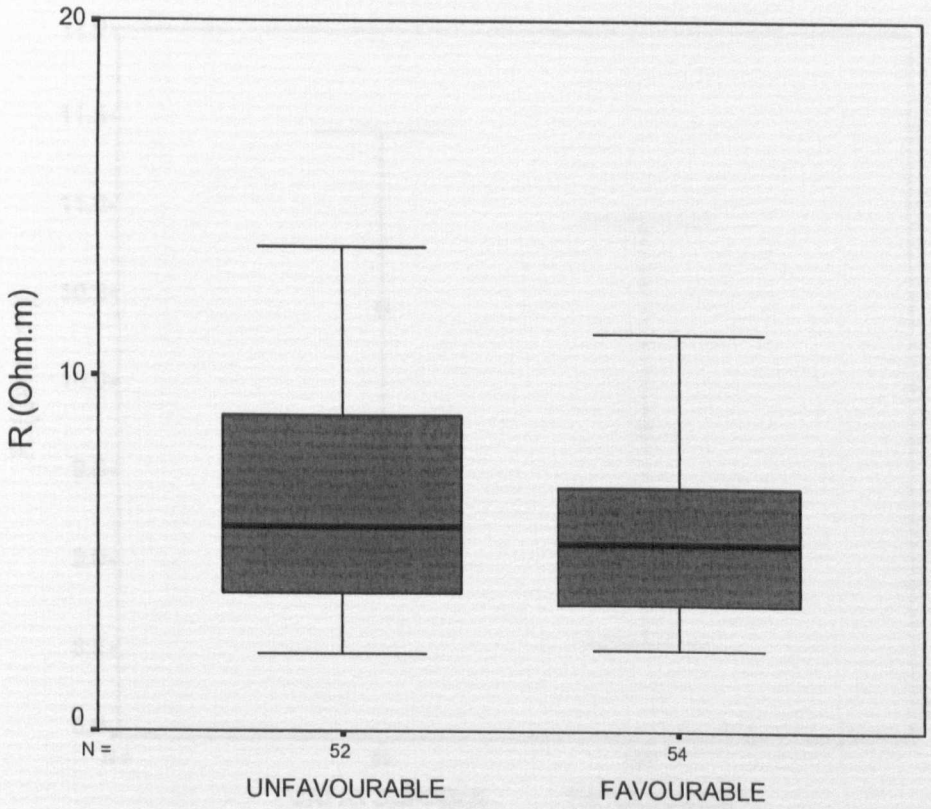

Figure 5.10 Extracellular Resistivity (R) measurements using the 8mm probe at the time of induction of labour. The median, interquartile range and the absolute range is shown. The two outlying values are excluded.

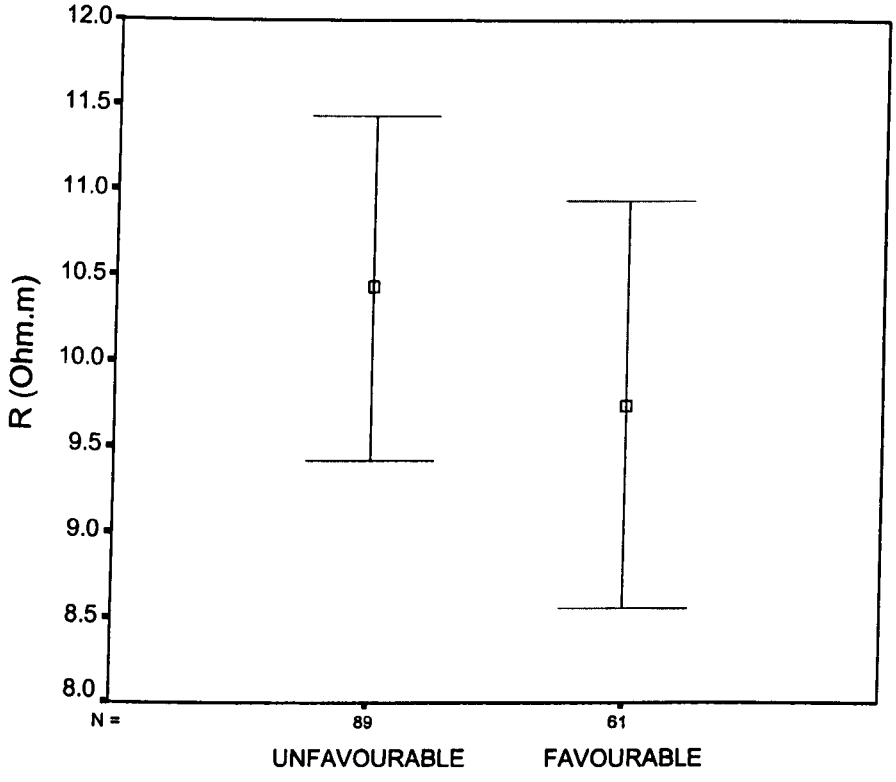

Figure 5.11 The mean +/- 2 standard errors of the mean extracellular resistivity (R) using the 5.5mm probe for the unfavourable and favourable cervices at the time of induction of labour.

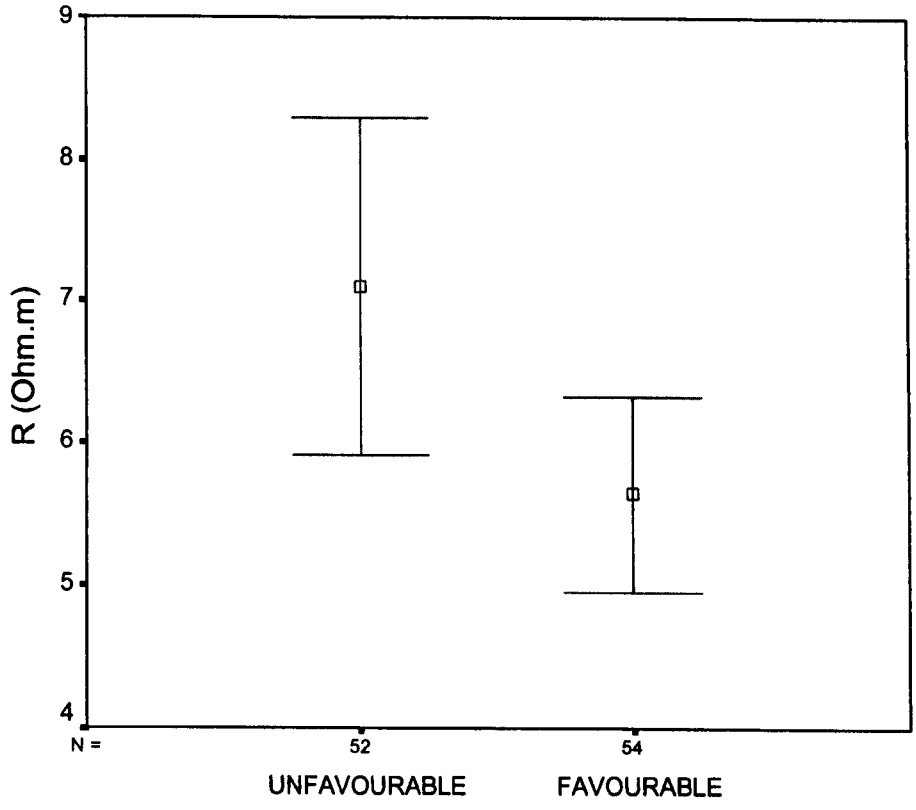

Figure 5.12 The mean +/- 2 standard errors of the mean extracellular resistivity (R) using the 8mm probe for the unfavourable and favourable cervices at the time of induction of labour.

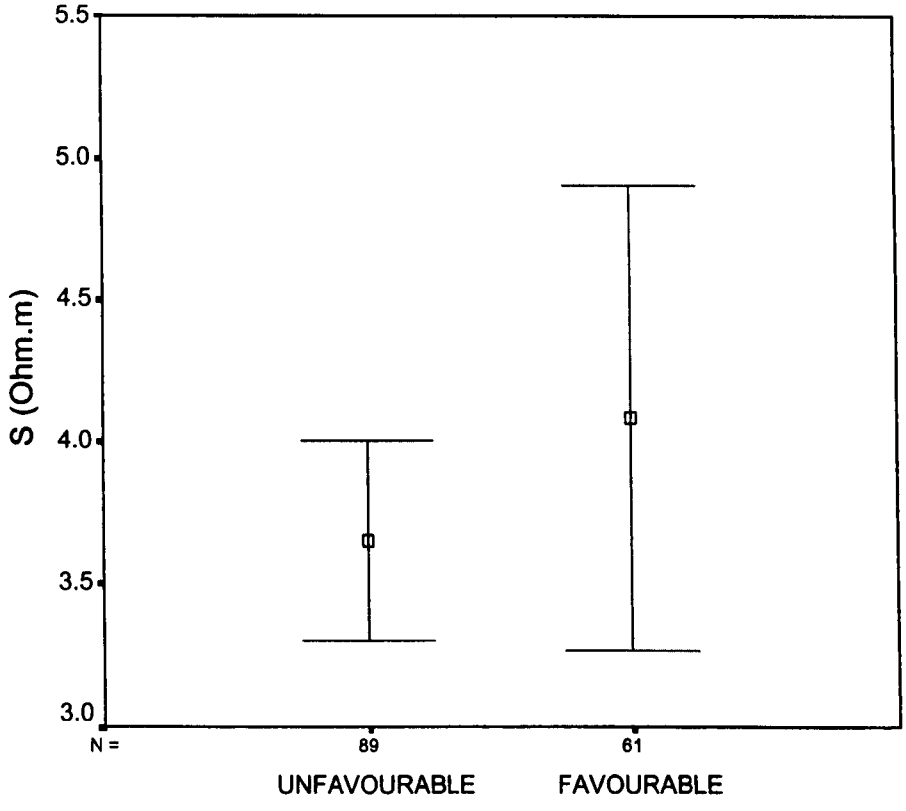

Figure 5.13 The mean +/- 2 standard errors of the mean intracellular resistivity (S) using the 5.5mm probe for the unfavourable and favourable cervices at the time of induction of labour.

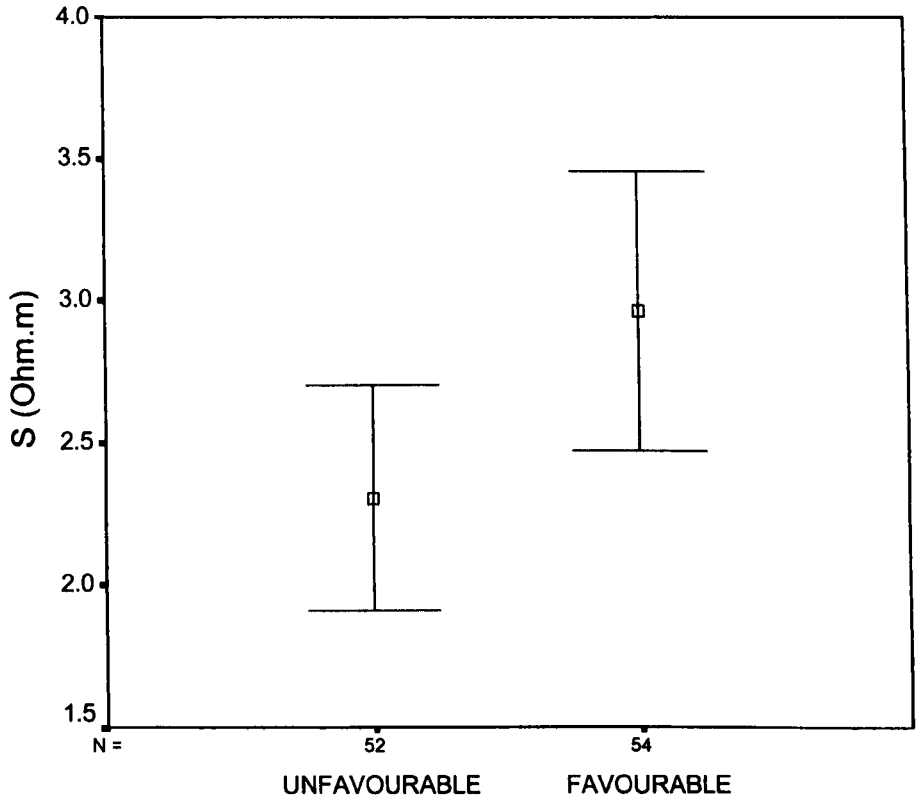

Figure 5.14 The mean +/- 2 standard errors of the mean intracellular resistivity (S) using the 8mm probe for the unfavourable and favourable cervices at the time of induction of labour.

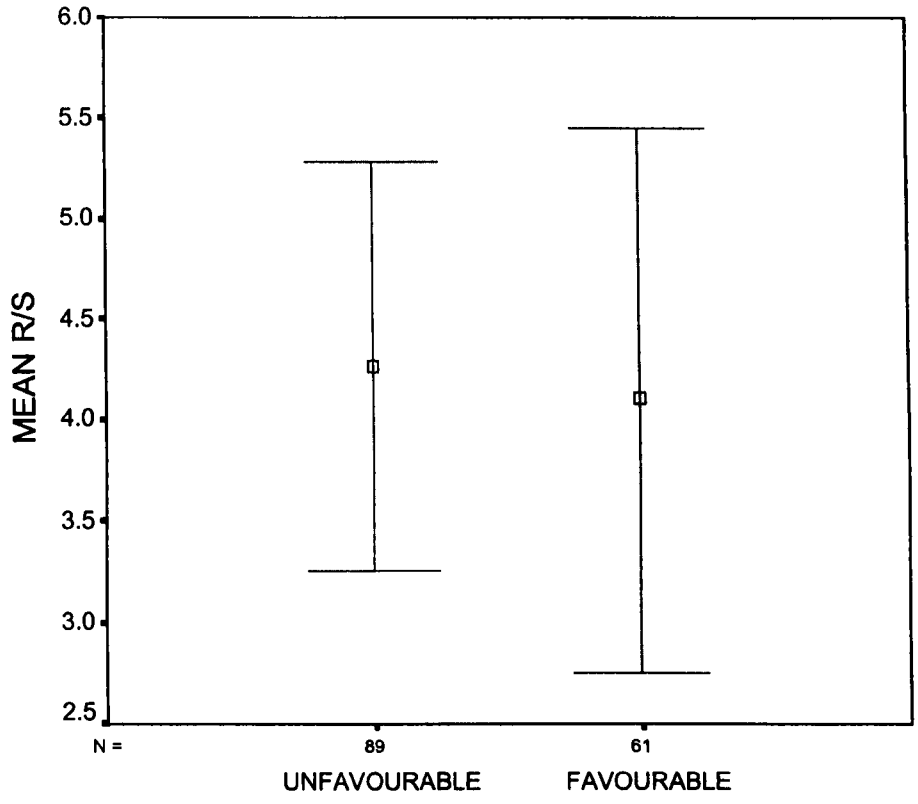

Figure 5.15 The mean +/- 2 standard errors of the mean extracellular to intracellular resistivity (R/S) using the 5.5mm probe for the unfavourable and favourable cervices at the time of induction of labour.

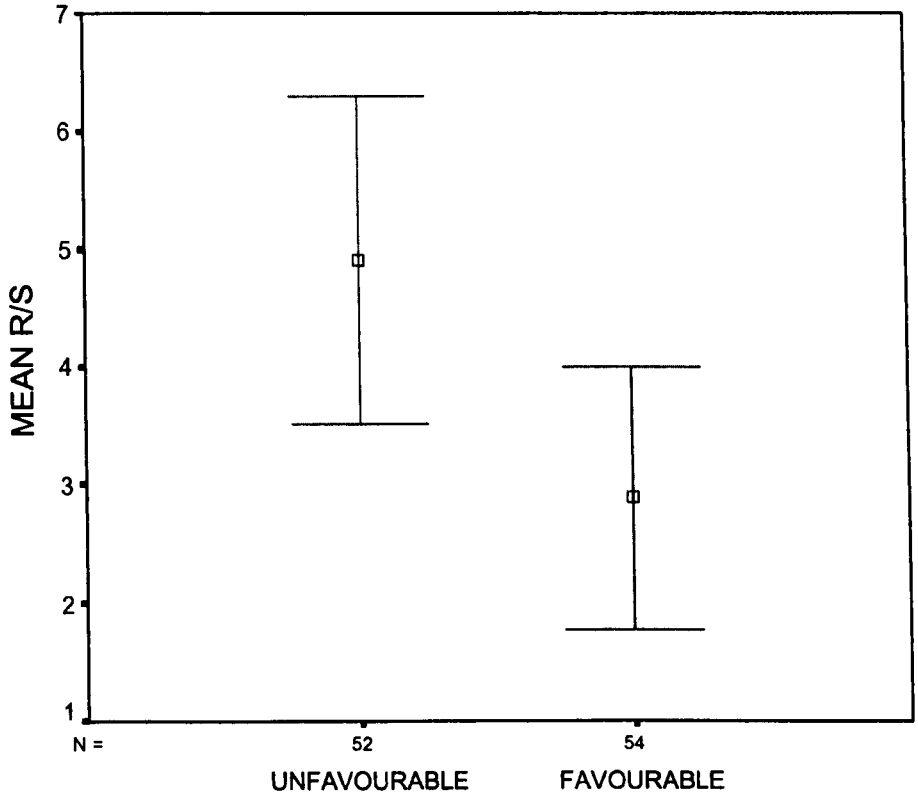

Figure 5.16 The mean +/- 2 standard errors of the mean extracellular to intracellular resistivity (R/S) using the 8mm probe for the unfavourable and favourable cervices at the time of induction of labour.

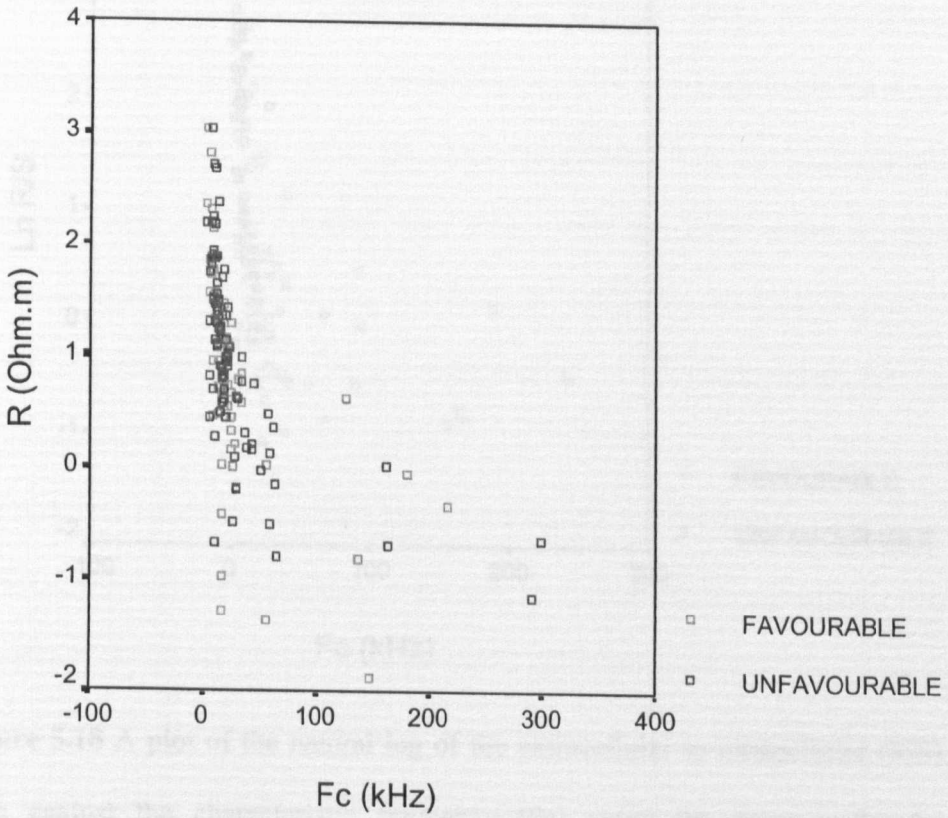

Figure 5.17 A plot of the natural log of the extracellular to intracellular (R/S) ratio against the characteristic frequency (Fc) using the 5.5mm probe for unfavourable and favourable cervices at induction of labour.

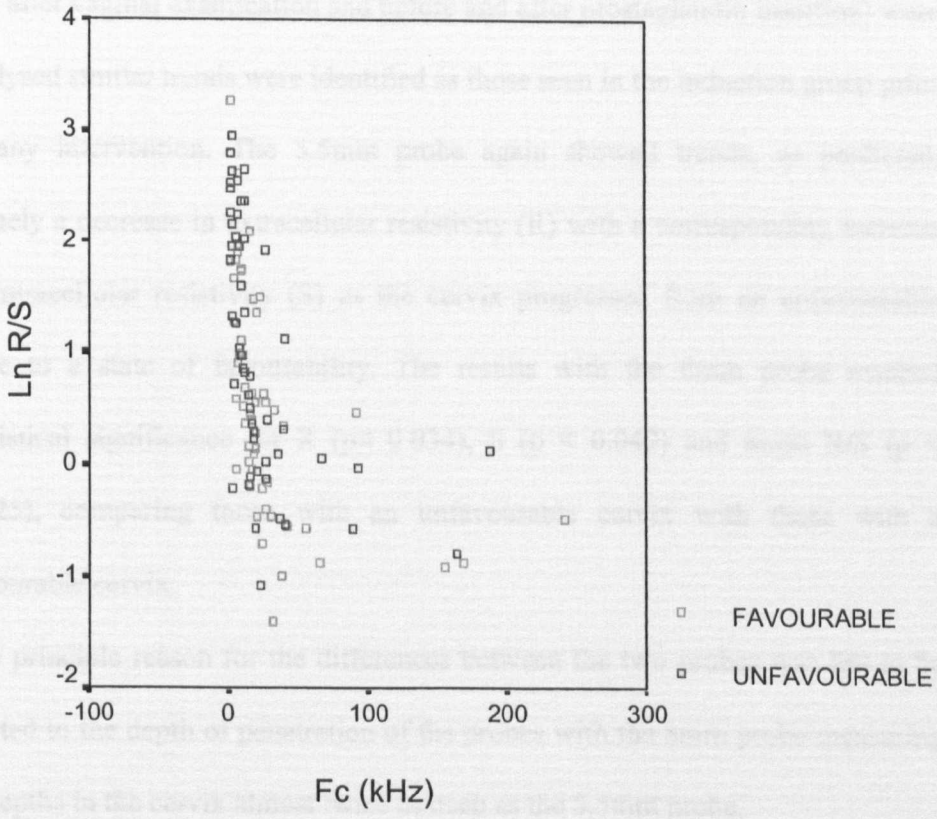

Figure 5.18 A plot of the natural log of the extracellular to intracellular (R/S) ratio against the characteristic frequency (Fc) using the 5mm probe for unfavourable and favourable cervices at induction of labour.

5.3.3 Discussion

When all the readings taken on women at the time of induction of labour (before and after vaginal examination and before and after prostaglandin insertion) were analysed similar trends were identified as those seen in the induction group prior to any intervention. The 5.5mm probe again showed trends, as predicted, namely a decrease in extracellular resistivity (R) with a corresponding increase in intracellular resistivity (S) as the cervix progressed from an unfavourable state to a state of favourability. The results with the 8mm probe reached statistical significance for R ($p< 0.034$), S ($p < 0.042$) and mean R/S ($p < 0.025$), comparing those with an unfavourable cervix with those with a favourable cervix.

The principle reason for the differences between the two probes was felt to be related to the depth of penetration of the probes with the 8mm probe measuring at depths in the cervix almost twice as deep as the 5.5mm probe.

It is noteworthy that the increase in R is not absolutely mirrored by the decrease in S as the cervix becomes more favourable. It would be incorrect to deduce from the data that the increase in R is only due to a fluid shift from the intracellular space (thereby increasing the intracellular resistivity S) to the extracellular space (thereby decreasing the extracellular resistivity R). The changes in R may also be in part related to the breakdown of collagen that occurs prior to labour onset, and may also be related to changes in cell orientation.

There is some separation of the unfavourable group from the favourable group when the LnR/S is plotted against the Fc values for both probes (figures.5.17, 5.18). However the data base is not large enough to allow differentiation of the favourable from the unfavourable group.

5.3.4 Summary

Whilst the 5.5mm probe demonstrated the expected trends, namely a decrease in extracellular resistivity with a corresponding increase in intracellular resistivity with increasing favourability of the cervix, these changes did not reach statistical significance. A statistically significant difference was seen in these parameters using the 8mm probe. This was most probably due to the greater depth of penetration of the 8mm probe.

The changes in extracellular resistivity measurements are not completely explained by the changes seen intracellular resistivity alone. They may be accounted for by fluid shifts from the intracelluar space to the extracellular space, changes in cell orientation and changes in collagen structure.

Thus it appears that the 8mm probe is a better discriminator of cervical favourability than the 5.5mm probe. This improved discrimination is almost certainly due to its ability to penetrate the cervical tissue to a deeper level.

5.4 TO ASSESS THE EFFECT OF INTRAVAGINAL PROSTAGLANDIN ON ELECTRICAL IMPEDANCE MEASUREMENTS OF THE CERVIX AT THE TIME OF INDUCTION OF LABOUR

5.4.1 Introduction

The role of prostaglandins in cervical ripening has been discussed in detail in 1.2.4a. Their effect on the cervix may be explained by alterations in glycosaminoglycan content that disperse and destabilise collagen fibrils and so increase tissue compliance. On that basis a decrease in extracellular resistivity (R) with an increase in intracellular resisitivity (S) is postulated if such a change in cervical compliance is found following prostaglandin application.

5.4.2 Patients and methods

The study was granted ethical approval by the Local Research Ethics Committee. All patients gave written informed consent prior to participating in the study. In obtaining consent it was highlighted to patients that participation in the study did not alter their clinical management and that if they wished to discontinue with the study following the initial readings, their induction of labour process would continue as per hospital protocol.

Transfer impedance measurements were obtained in the manner outlined at the beginning of this chapter using both the 5.5mm and 8mm probes.

A Bishop score was documented on all patients at the time of impedance measurements. If the Bishop score of ≤ 4 the cervix was deemed unripe and a prostaglandin pessary was inserted vaginally.

If the Bishop score of ≥ 5 the cervix was deemed ripe and thus suitable for an artificial rupture of the membranes.

5.4.3 Results

Using the 5.5mm probe 20 patients had an unripe cervix which remained unripe following prostaglandin insertion and a further 19 patients had an unripe cervix which subsequently ripened following prostaglandin. There was a trend towards an increase in extracellular resistivity with less ripe cervices, with a mean resistivity of 8.79 Ωm in the unripe group which subsequently ripened, and a mean resisitivity of 9.91Ωm and 10.27Ωm in the groups that were initially unripe and did not ripen following prostaglandin respectively (figure 5.19). These changes did not reach statistical significance. Similarly there was a trend towards a decrease in intracellular resistivity with less ripe cervices, with a mean resistivity of 4.06Ωm in the unripe group which subsequently ripened, and a mean resisitivity of 3.71Ωm and 3.18Ωm in the groups that were initially unripe and did not ripen following prostaglandin respectively (figure 5.21). Again these changes did not reach statistical significance. The means, standard deviations, ranges are summarised in Table 5.5.

Using the 8mm probe the cervix remained unripe following prostaglandin insertion in 12 patients and the cervix ripened in a further 15 patients. The effects of prostaglandin insertion on extracellular resistivity and intracellular resistivity are demonstrated in figures 5.20 and 5.22. Whilst the means show some trends, namely an tendency to increase the extracellular resistivity with less ripe cervices and a fall in intracellular resisitvity associated with less ripe

cervices, the amount of crossover is far too great to reach either statistical or clinical significance. The means, standard deviations, ranges are summarised in Table 5.6.

Figures 5.23 and 5.25 demonstrate the effect of prostaglandin on extracellular resistivity using the 5.5mm probe in those patients whose cervix ripened post-prostaglandin and those whose cervix failed to ripen post-prostaglandin. A trend towards an increased interval to delivery was seen in those whose cervix ripened but whose extracellular resistivity increased compared to those whose extracellular resistivity decreased following prostaglandin insertion, with a mean interval to delivery of 1577 minutes and 1343 minutes respectively. This difference did not reach statistical significance (p =0.194 independent sample t test). A similar trend was noted in those whose cervix was ripe post-prostaglandin, in that those whose extracellular resisitivity decreased had a mean interval to delivery of 707 minutes versus those whose extracellular resisitivity increased having a mean interval to delivery of 852 minutes. Again this difference did not reach statistical significance (p=0.397 independent sample t test). Similar trends were seen using the 8mm probe (figures 5.24 and 5.26). The mean interval to delivery was 1261minutes when the extracellular resistivity decreased versus 1698 minutes when the extracellular resistivity increased for those whose cervix ripened with prostaglandin (p=0.091 independent sample t test) and 542 minutes when the extracellular resistivity decreased following prostaglandin insertion *versus* 967 minutes when the extracellular resistivity increased following prostaglandin insertion in those whose cervix was ripe (p=0.087 independent sample t test).

RIPEN		R	S	RDIVS	FC
1.00	Mean	8.7931	4.0631	.7244	35.7000
	N	19	19	19	19
	Std. Deviation	3.0996	1.6302	.6342	36.1853
	Median	10.2287	3.8599	.8400	19.5400
	Minimum	3.82	2.02	-.80	5.41
	Maximum	13.22	8.37	1.76	162.23
	Range	9.40	6.35	2.56	156.82
2.00	Mean	9.2936	4.3265	.8175	17.1200
	N	19	19	19	19
	Std. Deviation	4.5270	4.3063	.9807	7.4528
	Median	8.8855	3.3100	.8380	16.7900
	Minimum	2.38	1.03	-1.28	2.31
	Maximum	21.59	21.13	3.03	32.82
	Range	19.21	20.10	4.31	30.51
3.00	Mean	9.9067	3.7137	.9138	19.7995
	N	20	20	20	20
	Std. Deviation	4.6490	1.2145	.7480	13.8362
	Median	10.4353	3.8387	.8892	14.0300
	Minimum	1.82	.50	-.68	5.18
	Maximum	19.63	5.79	2.37	50.03
	Range	17.81	5.29	3.05	44.85
4.00	Mean	10.2652	3.1790	1.1315	35.9873
	N	20	20	20	20
	Std. Deviation	4.4982	1.8237	.9343	69.3169
	Median	11.4685	2.6805	1.4057	10.9225
	Minimum	2.27	.91	-1.16	1.79
	Maximum	20.56	7.10	2.67	291.96
	Range	18.29	6.20	3.83	290.17

Table 5.5 Effect of prostaglandin on cervix at induction of labour using 5.5mm probe.

R= Extracellular resistivity, S= Intracellular resisitivity, RDIVS= Natural log of extracellular divided by intracellular resisitivity, Fc = Characteristic frequency.

RIPEN 1= Unripe pre-prostaglandin but ripened, RIPEN 2 = Ripe post-prostaglandin,

RIPEN 3 = Unripe pre-prostaglandin, remained unripe, RIPEN 4 = Unripe post-prostaglandin.

RIPEN		R	S	RDIVS	Fc
1.00	Mean	6.0496	3.1718	.6342	38.5593
	N	15	15	15	15
	Std. Deviation	2.9755	1.2044	.9608	41.1027
	Median	5.5610	3.3164	.7305	26.5300
	Minimum	2.17	.52	-.53	1.97
	Maximum	11.15	5.17	3.06	164.62
	Range	8.98	4.64	3.59	162.65
2.00	Mean	6.0055	2.9901	.7378	23.0567
	N	15	15	15	15
	Std. Deviation	2.8698	1.9113	.9167	20.4319
	Median	4.3694	2.5800	.7217	18.0200
	Minimum	2.91	1.06	-1.11	6.90
	Maximum	10.99	8.83	2.20	91.68
	Range	8.08	7.77	3.31	84.78
3.00	Mean	6.2339	2.5709	1.0539	12.0629
	N	12	12	12	12
	Std. Deviation	3.0650	1.8226	1.1530	7.3983
	Median	5.2831	2.1150	1.0275	13.0600
	Minimum	2.78	.62	-.82	1.72
	Maximum	12.40	6.34	2.51	22.55
	Range	9.62	5.72	3.33	20.83
4.00	Mean	7.1589	1.8818	1.4500	11.2479
	N	12	12	12	12
	Std. Deviation	3.4576	1.1568	1.0650	9.3062
	Median	6.7527	1.8227	1.2217	10.5650
	Minimum	2.27	.41	-.17	1.75
	Maximum	13.64	3.65	2.89	34.98
	Range	11.37	3.24	3.06	33.23

Table 5.6 Effect of prostaglandin on cervix at induction of labour using 8mm probe.

R= Extracellular resistivity, S= Intracellular resisitivity, RDIVS= Natural log of extracellular divided by intracellular resisitivity, Fc = Characteristic frequency.

RIPEN 1= Unripe pre-prostaglandin but ripened, RIPEN 2 = Ripe post-prostaglandin,

RIPEN 3 = Unripe pre-prostaglandin, remained unripe, RIPEN 4 = Unripe post-prostaglandin.

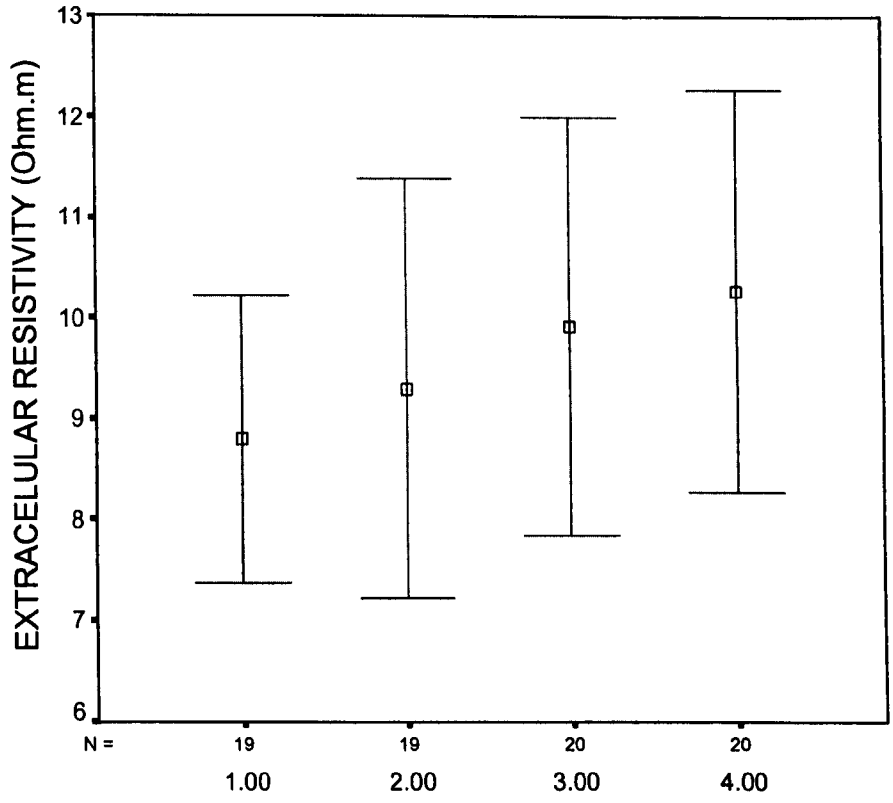

Figure 5.19 Effect of prostaglandin (PG) on extracellular resisitivity (mean +/- 2 Standard Errors of Mean) 5.5mm probe.

1.00= Unripe and ripened post PG, 2.00= Ripe post-PG.

3.00= Unripe and remained unripe post-PG, 4.00= Unripe post-PG.

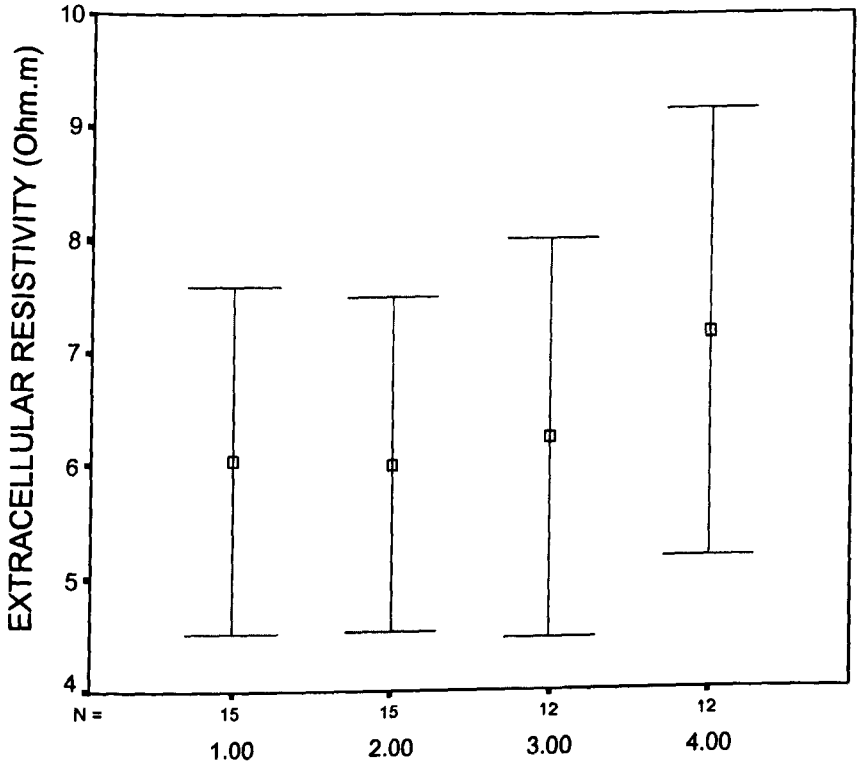

Figure 5.20 Effect of prostaglandin (PG) on extracellular resisitivity (mean +/- 2 Standard Errors of Mean) 8mm probe.

1.00= Unripe and ripened post PG, 2.00= Ripe post-PG.

3.00= Unripe and remained unripe post-PG, 4.00= Unripe post-PG.

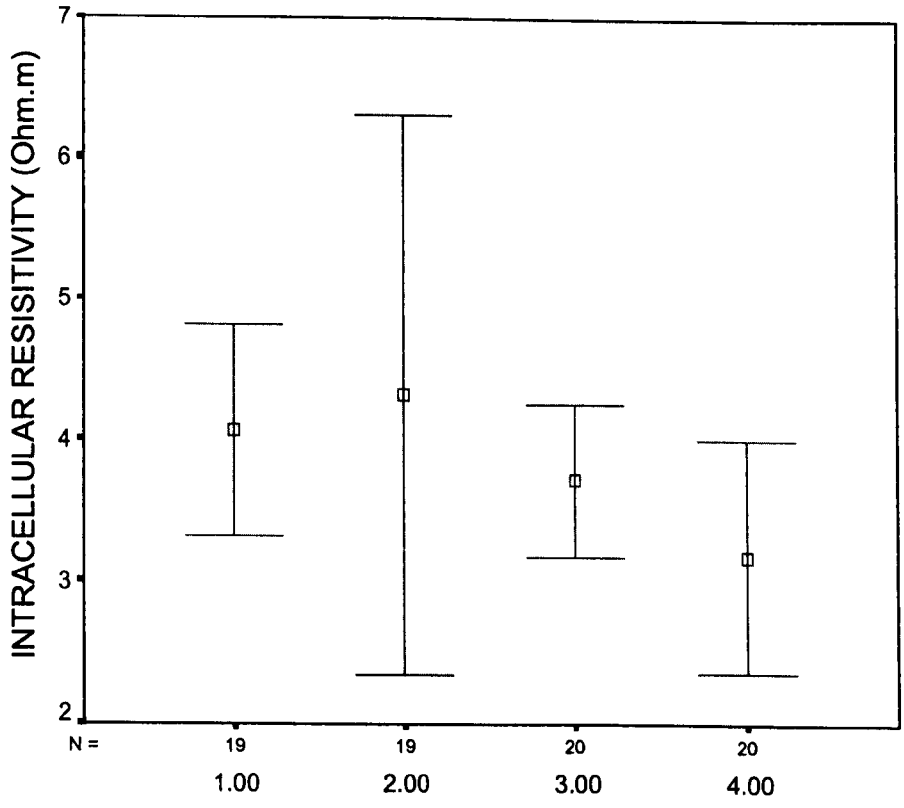

Figure 5.21 Effect of prostaglandin (PG) on intracellular resisitivity (mean +/- 2 Standard Errors of Mean) 5.5mm probe.

1.00= Unripe and ripened post PG, 2.00= Ripe post-PG.

3.00= Unripe and remained unripe post-PG, 4.00= Unripe post-PG.

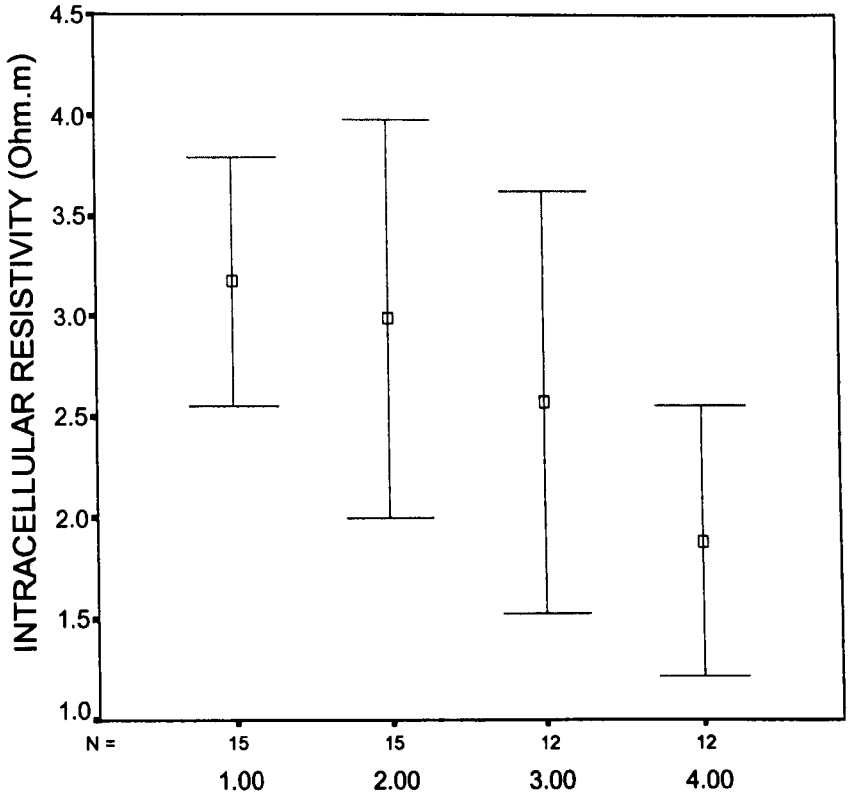

Figure 5.22 Effect of prostaglandin on intracellular resisitivity (mean +/- 2 Standard Errors of Mean) 8mm probe.

1.00= Unripe and ripened post PG, 2.00= Ripe post-PG.

3.00= Unripe and remained unripe post-PG, 4.00= Unripe post-PG.

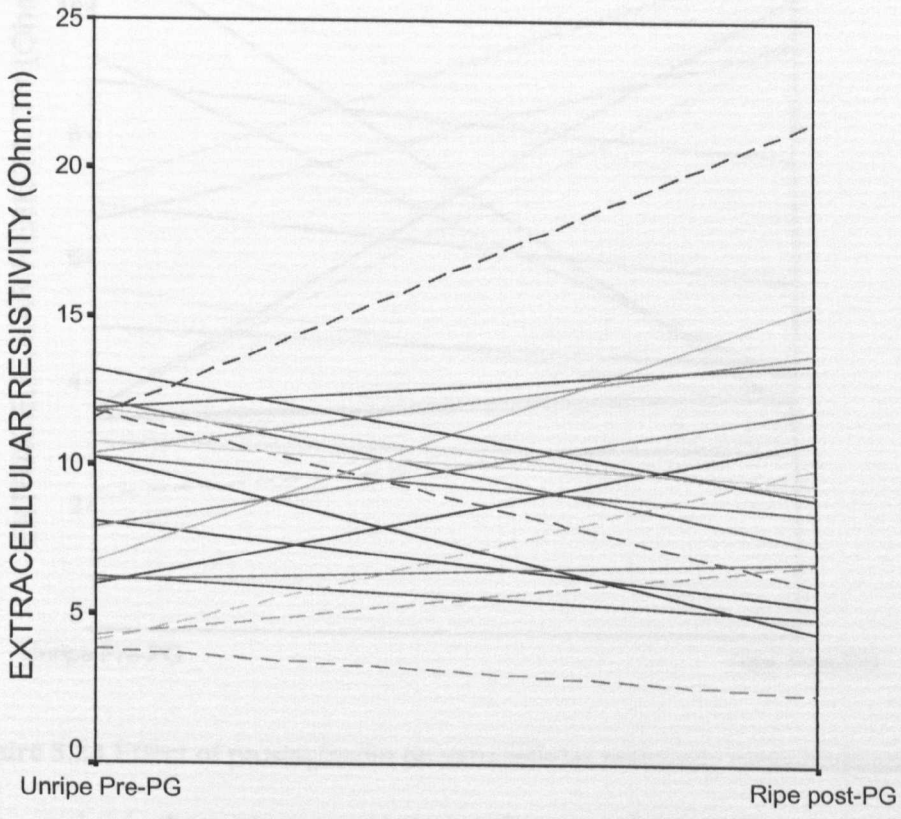

Figure 5.23 Effect of prostaglandin on extracellular resistivity measurements (5.5mm probe) in those whose cervix ripened following the insertion of prostaglandin.

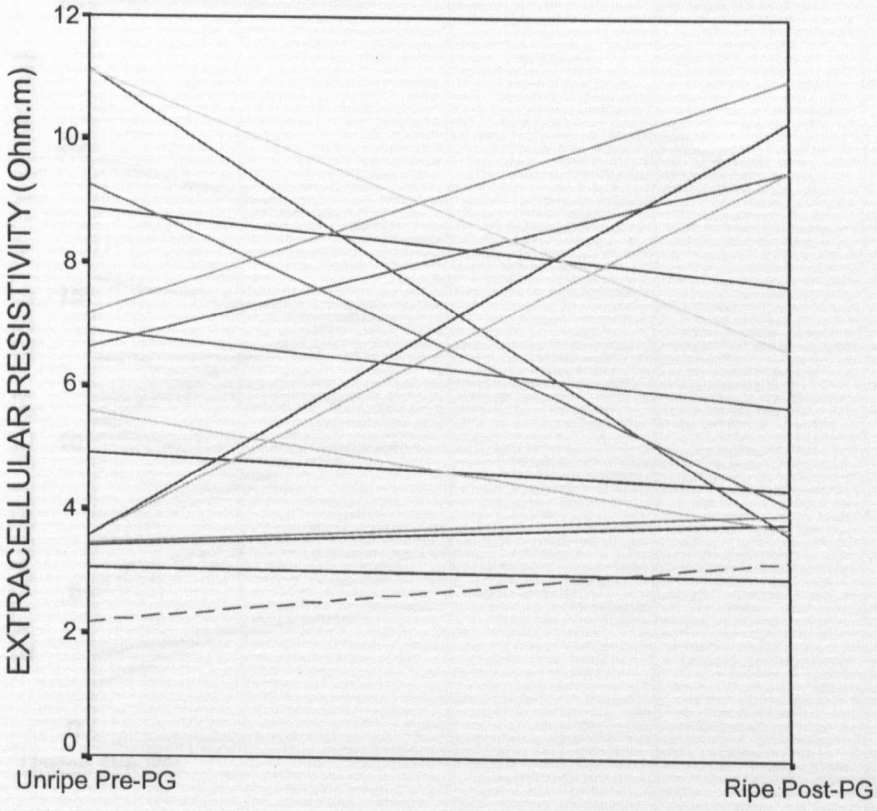

Figure 5.24 Effect of prostaglandin on extracellular resistivity measurements (8mm probe) in those whose cervix ripened following the insertion of prostaglandin.

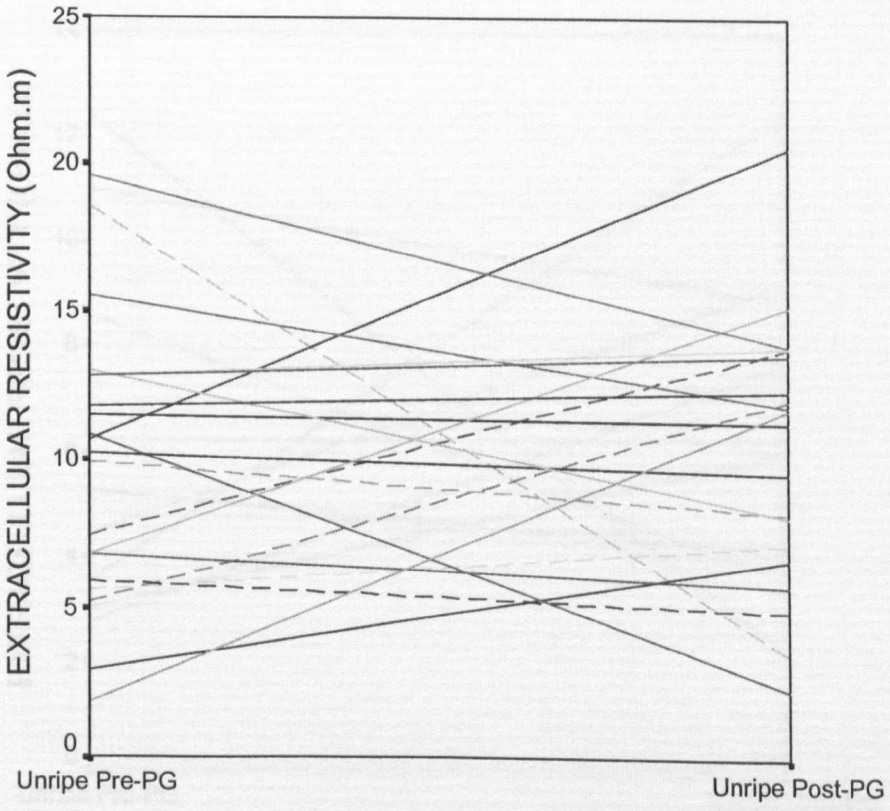

Figure 5.25 Effect of prostaglandin on extracellular resistivity measurements (5.5mm probe) in those whose cervix failed to ripen following the insertion of prostaglandin.

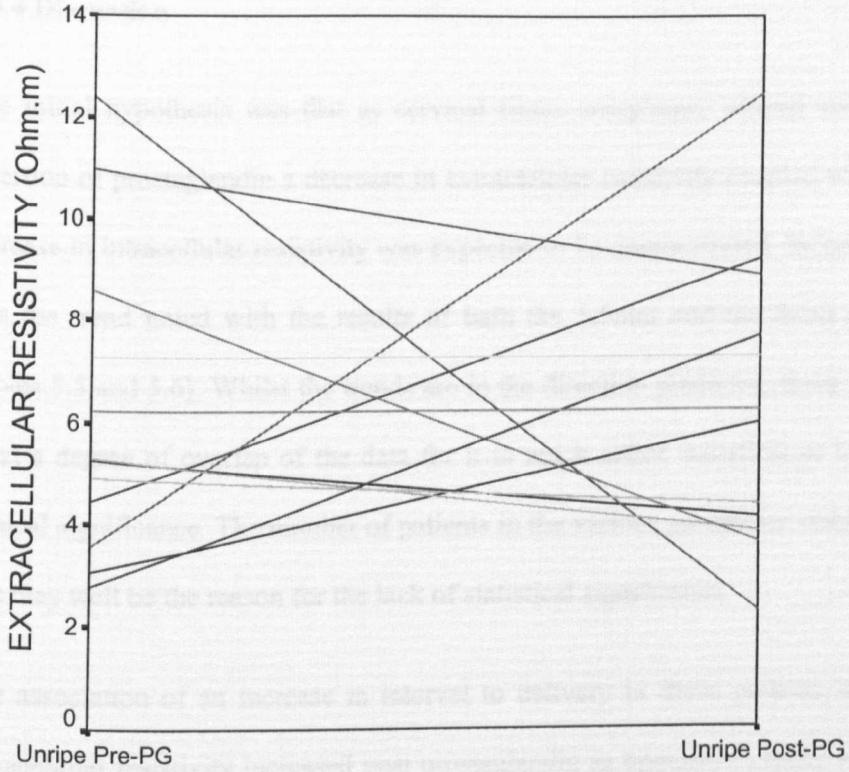

Figure 5.26 Effect of prostaglandin on extracellular resistivity measurements (8mm probe) in those whose cervix failed to ripen following the insertion of prostaglandin.

5.4.4 Discussion

The initial hypothesis was that as cervical tissue compliance altered with the insertion of prostaglandin a decrease in extracellular resistivity coupled with an increase in intracellular resistivity was expected to be demonstrated. Indeed this was the trend noted with the results of both the 5.5mm and the 8mm probe (tables 5.5 and 5.6). Whilst the trends are in the direction predicted, there is too great a degree of overlap of the data for it to reach either statistical or indeed clinical significance. The number of patients in the various groups are small and this may well be the reason for the lack of statistical significance.

The association of an increase in interval to delivery in those patients whose extracellular resistivity increased post prostaglandin as opposed to those whose extracellular resistivity decreased is noteworthy. It is unlikely to be due to a calibration problem as the probes were calibrated with one tenth normal saline on a daily basis. Likewise all the measurements were performed by the same operator and so inter-observer variation is not an issue. In some cases remnants of the prostaglandin pessary were found in the vagina at the follow-up examination. These were avoided when placing the probes on the cervix and so we feel would not affect the readings. An inherent difference, in the response of the cervix whose extracellular resistivity increased in response to prostaglandin insertion as opposed to the cervix whose extracellular resistivity decreased, is postulated. This finding has not been described previously and deserves further study particularly with larger number to ascertain if indeed it is a real rather than apparent finding.

5.4.5 Summary

The changes already demonstrated in extracellular resistivity and intracellular resistivity were still apparent although not statistically significant in this section of the study. It was not possible to correlate the resistivity readings with the degree of cervical ripeness seen clinically. This is most likely due to the fact that clinical assessment of cervical ripeness using the bishop score includes such parameters as station of the fetal head, cervical dilatation and position of the cervix which are not measured by resistivity measurements. These disadvantages may well be allayed by the objectivity of the resistivity measurements. Interestingly if on subsequent measuring the extracellular resistivity decreased then the patient was more likely to have a shorter interval to delivery. This may be due to an inherent difference in the cervix itself which has not previously been documented

This study has demonstrated an inherent difference in extracellular resistivity of the cervix which is associated with interval to delivery time differences.

5.5 THE PREDICTION OF INTERVAL TO LABOUR, DURATION OF THE FIRST STAGE OF LABOUR, INTERVAL TO DELIVERY AND DELIVERY OUTCOME USING ELECTRICAL IMPEDANCE MEASUREMENTS OF THE CERVIX AT THE TIME OF INDUCTION OF LABOUR.

5.5.1 Introduction

The potential clinical value of electrical impedance measurements lies in their ability to predict induction of labour to delivery interval. Such prediction would allow for a more scientific basis for offering induction of labour and avoiding induction of labour in those patients at a high risk of failure. It could be of particular value in situations where patients request induction of labour on non-medical grounds and so allow for better informed consent.

In this section electrical impedance measurements are correlated with onset of labour, length of the first stage of labour, induction to delivery interval and mode of delivery.

5.5.2 Patients and methods

In this study 107 women underwent assessment, at the time of induction of labour, using the 5.5mm tetrapolar probe, 8 women were excluded from the analysis as the gain was too low and thus yielded unreliable readings. Of the 99 women included in the analysis 39 had two sets of readings and 6 had three sets

of readings, giving 150 sets of readings for analysis in the 5.5mm probe group. A total of 86 women were assessed using the 8mm probe, with 12 excluded as the gain was too low thereby yielding unreliable readings. Of the 74 women included for analysis 28 had two sets of readings and 2 had three sets of readings, giving 106 sets of readings for analysis in the 8mm probe group.

Initially all patients had a Cusco speculum examination and transfer impedance measurements were made at a frequency of 4.8kHz using a 5.5mm and 8mm diameter pencil probes. The probes were placed on the surface of the cervix and a current of 10 μA was passed between an adjacent pair of electrodes and the resulting potential measured between the remaining pair. This was followed by a digital vaginal examination, at which time a Bishop score was determined. All examinations were perfromed by the same operator, who was blinded to the electrical impedance results.

5.5.3 Results

Descriptive data of patients who were enrolled in the study is shown in tables 5.7 and 5.8. The difference in the number of readings is due to the fact that we commenced the study with the 5.5mm probe prior to using the 8mm probe.

Using the 5.5mm probe no correlation was noted with either extracellular or intracellular resistivity and length of the first stage of labour, Bishop score or delivery outcome. The natural logarithmic transformation of the extracellular/intracellular resistivity was correlated with interval to labour (Pearson correlation 0.173) and with the interval to delivery (Pearson correlation

0.196). In both cases the correlation was significant at the 0.05 level. The Bishop score correlated with both interval to labour (Pearson correlation -0.418) and with interval to delivery (Pearson correlation -0.440) and the correlations were significant to the 0.01 level. The Bishop score was also correlated with the length of the first stage of labour (Pearson correlation -0.204). This correlation was significant at the 0.05 level. Receiver Operator curves derived from data for normal delivery and Caesarean section for failed induction and failure to progress in the first stage of labour demonstrated an area under the curve for extracellular resistivity of 0.592 and 0.399 for the Bishop score (figures 5.27 and 5.29).

Using the 8mm probe both extracellular resistivity and the natural logarithmic transformation of the extracellular/intracellular resistivity were correlated with interval to delivery with Pearson correlation factors of 0.42 and 0.257 respectively. The former correlated siginificantly at the 0.01 level and the latter correlated significantly at the 0.05 level. The Bishop score correlated with interval to delivery (Pearson correlation -0.431, correlating significantly at 0.01 level) and length of the first stage of labour (Pearson correlation -0.255, correlating significantly at the 0.05 level). Receiver Operator curves derived from data for normal delivery and Caesarean section for failed induction and failure to progress in the first stage of labour demonstrated an area under the curve for extracellular resistivity of 0.661 and 0.384 for the Bishop score (figures 5.28 and 5.30).

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	150	16.00	46.00	26.6467	6.5836
PARITY	150	.00	5.00	.9533	1.1489
GESTATION	150	34.00	42.00	40.0333	1.8732
Valid N (listwise	150				

Table 5.7 Descriptive data of patients at induction of labour who underwent electrical impedance measurements using the 5.5mm probe.

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
AGE	106	16.00	46.00	25.8396	6.3021
PARITY	106	.00	5.00	.8113	1.0964
GEST	106	34.00	42.00	40.2453	1.8762
Valid N (listwi	106				

Table 5.8 Descriptive data of patients at induction of labour who underwent electrical impedance measurements using the 8mm probe.

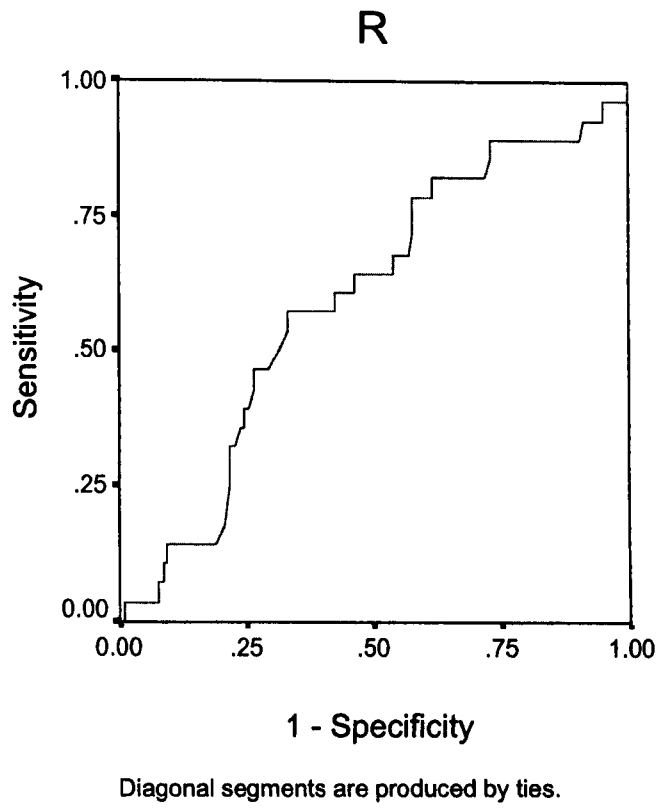

Figure 5.27 Receiver operator curve (ROC) derived from data (5.5mm probe) for normal vaginal delivery and Caesarean section for either failed induction of labour or failure to progress. Area under the curve 0.592.

R= Extracellular resistivity

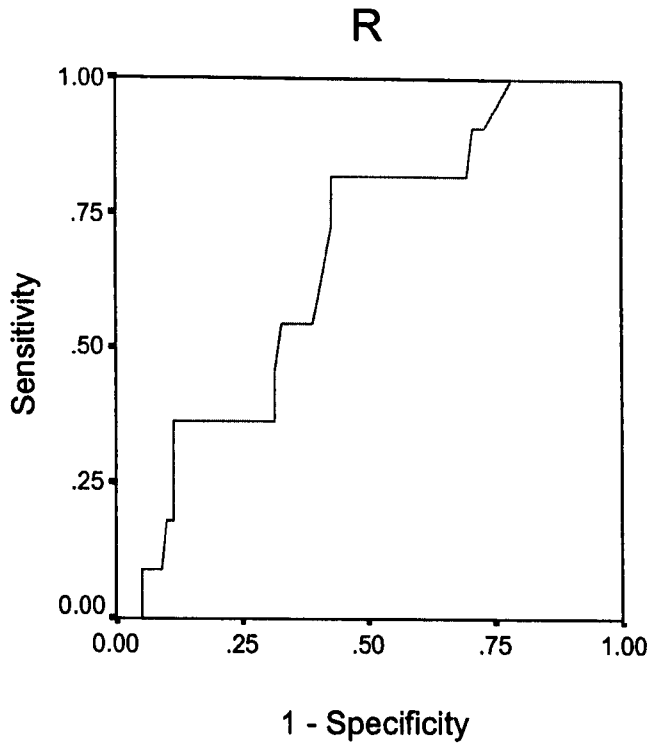

Figure 5.28 Receiver operator curve (ROC) derived from data (8mm probe) for normal vaginal delivery and Caesarean section for either failed induction of labour or failure to progress. Area under the curve 0.661.

R= Extracellular resisitvity

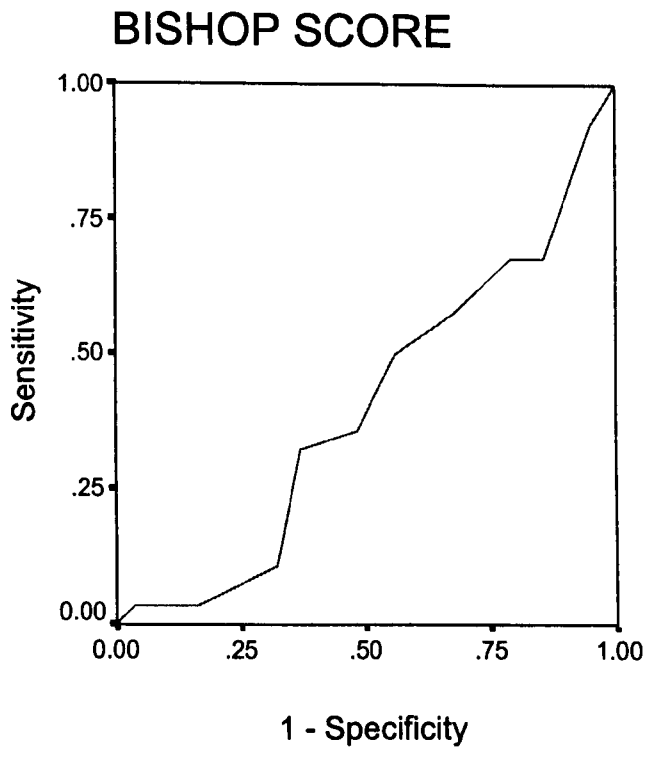

Figure 5.29 Receiver operator curve (ROC) curve derived from data (5.5mm probe) for normal vaginal delivery and Caesarean section for either failed induction of labour or failure to progress, using Bishop score. Area under the curve 0.399.

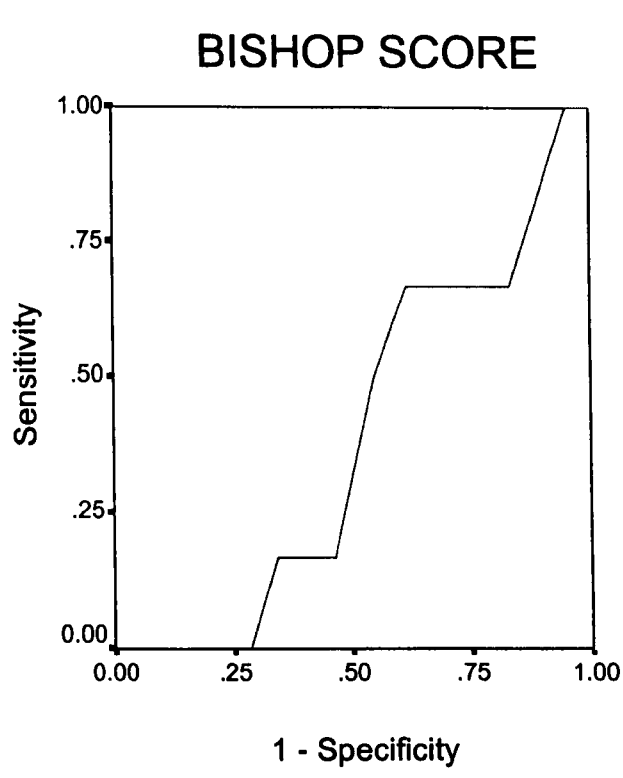

Figure 5.30 Receiver operator curve (ROC) curve derived from data (8mm probe) for normal vaginal delivery and Caesarean section for either failed induction of labour or failure to progress,using the Bishop score. Area under the curve 0.384.

5.5.4 Discussion

As the data assumed a near normal distribution it was decided to perfrom Pearson correlations on the electrical impedance measurements and Bishop score with regard to interval to labour, length of the first stage of labour and interval to delivery. Interestingly the Bishop score showed statistically significant correlations with all three parameters measured using the 5.5mm probe cohort but only showed statistically significant correlations with interval to delivery and length of the first stage of labour using the data for the 8mm probe cohort. The electrical impedance measurements demonstrated statistically significant correlations with interval to delivery but these were seen only with the extracellular resistivity and the natural logarithmic transformation of the extracellular/intracellular resistivity measurements. In Hull Maternity Hospital the diagnosis of labour in patients undergoing induction of labour is often made on a need for analgesia basis and not on more robust criteria such as cervical dilatation. Hence the interval to labour and indeed the starting point of the first stage of labour is subjective. The interval to delivery is a more robust parameter as there is an obvious end point. To assess the usefulness of extracellular resistivity and the Bishop score as a screening test, we dervied receiver operator curves for normal vaginal delivery and Caesarean section with failed induction or failure to progress in the first stage of labour as its indication (figures 5.27, 5.28, 5.29, 5.30). Receiver operator curves show the sensitivities (1 minus the fraction of false negative results) and specificities (1 minus the fraction of false positive results) obtained with these variables used as discriminants between the

normal vaginal delivery group and the Caesarean section (failed induction, failure to progress in the first stage) group. If the measurements give no discrimination between the two groups, a single line at 45^0 is obtained. If there is a discrimination, the curve is displaced upwards and to the left. The area under the curve indicates the degree of separation: an area of 0.5 corresponds to no discrimination between the groups and an area of 1.0 to perfect discrimination. The extracellular resistivity performed better than the Bishop score in discriminating between the groups, and the 8mm probe performed better than the 5.5mm probe. This was most likely due to the greater depth of penetration of the cervix with the 8mm probe.

One should however interpret these results with caution as the numbers of patients in the Caesarean section group was only 28 in the 5.5mm probe group and 11 in the 8mm probe group.

A larger study is clearly needed to clarify these results.

5.5.5 Summary

This study demonstrates that the Bishop score correlates better with the subjective measures of interval to labour and length of the first stage of labour, whereas the electrical impedance measurements correlate as well if not marginally better with the more objective measure of interval to delivery and delivery outcome. The extracellular resistivity discriminates better than the Bishop score in identifiying those who will eventually have a Caesarean section

for either failed induction or failure to progress in the first stage of labour. However the area under the curve needs to be brought closer to one for the extracellular resistivity to be of value in a screening situation.

This study highlights the potential value of electrical impedance measurements as a predictor of pregnancy outcome and in particular its objective nature in predicting these outcomes.

5.6 CONCLUSIONS

The induction of labour studies have demonstrated that prior to any intervention the 8mm probe performed better than the 5.5mm probe and that this was almost certainly due to the ability of the 8mm probe to penetrate to a greater depth in the cervix.In the study that included both pre- and post- intervention readings the 8mm probe again performed better than the 5.5mm probe. The 8mm probe discriminated the favourable from the unfavourable cervix with greater precision but this discriminatory effect did not reach statistical significance.The study looking at the effect of prostaglandin on the electrical impedance readings of the cervix revealed an inherent difference in the extracellular resistivity of the cervix which is associated with differences in interval to delivery times.The final induction study highlighted the potential value of electrical impedance measurements as a predictor of pregnancy outcome and in particular its objective nature in predicting these outcomes.We accept that our numbers are small, but the findings outlined would support further larger studies in this area.

CHAPTER 6

ELECTRICAL IMPEDANCE MEASUREMENTS OF THE POST-PARTUM CERVIX

6.1 INTRODUCTION

This study aimed to assess the re-modelling process in the post-partum cervix. It is known that the role of the cervix in the post-partum period is to prepare itself for a future pregnancy. The hypothesis was that if the resisitivity measurements decreased approaching term then an increase in the post-partum period would be expected. Whether they would ever reach the original pre-pregnancy levels is uncertain.

This study also aimed to characterise the speed of the re-modelling process.

6.2 PATIENTS AND METHODS

Patients were recruited from both the post-natal wards and post-natal clinic for this study with 15 patients participating in the study using the 5.5mm probe and 11 in the study using the 8mm probe. Each gave written informed consent prior to undergoing the measurements. The measurements were taken in the standard manner by placing the probe on the surface of the cervix and passing a current of 10 μA between the adjacent pair of electrodes and measuring the resulting potential between the remaining pair. A set of measurements was collected in 15ms and at each point on the cervix 100 sets were recorded and the average calculated. Each patients had at least four sets of readings. Only readings taken at the 4.8 kHz frequency were used for the analysis. All readings were taken by a single operator.

The post-partum resistivity readings were then compared with the resistivity readings taken on the 195 women in the colposcopy clinic and the 78 readings taken at induction of labour prior to any intervention as described in chapter 4.

6.3 RESULTS

In the 5.5mm probe study the mean parity was 1.47 (range 0-4), mean age 29.1years (range 17-42 years), mean number of days post-partum 20 (range 1-54) and mean resistivity 10.76 Ωm (range 4.24 - 23.56 Ωm). Of the 15 patients, 5 had either an elective Caesarean section or a Caesarean section for fetal distress, with a further 5 patients having a normal vaginal delivery and the remaining 5 having a Caesarean section either for failure to progress or failed induction. No difference was noted in the resistivity measurements between the three groups studied. Of the group studied 4 patients had sequential readings and their results are shown in figure 6.1.

In the 8mm study the mean parity was 1.29 (range 0-4), mean age 31.1years (range 17-42 years), mean number of days post-partum 19.8 (range 2-54) and mean resistivity 4.56 Ωm (range 2.07 - 9.04 Ωm). Of the 11 patients 5 had either an elective Caesarean section or a Caesarean section for fetal distress, with a further 3 patients having a normal vaginal delivery and the remaining 3 having a Caesarean section either for failure to progress or failed induction.Againo difference was noted in the resistivity readings between the three groups studied. Of the group studied 3 patients had sequential readings and their results are shown in figure 6.2.

Comparing the pregnant and post-partum patients no statistically significant difference is identified (figure 6.3).

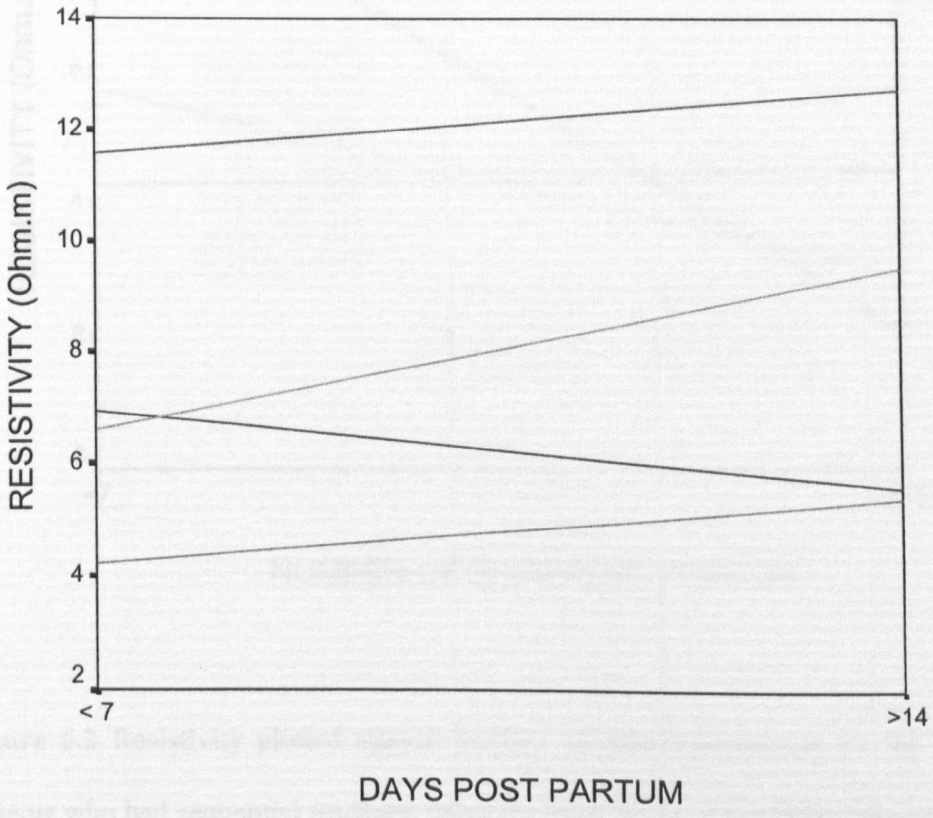

Figure 6.1 Resistivity plotted against number of days post-partum for the 4 patients who had sequential readings, using the 5.5mm probe. Each line represents an individual patient.

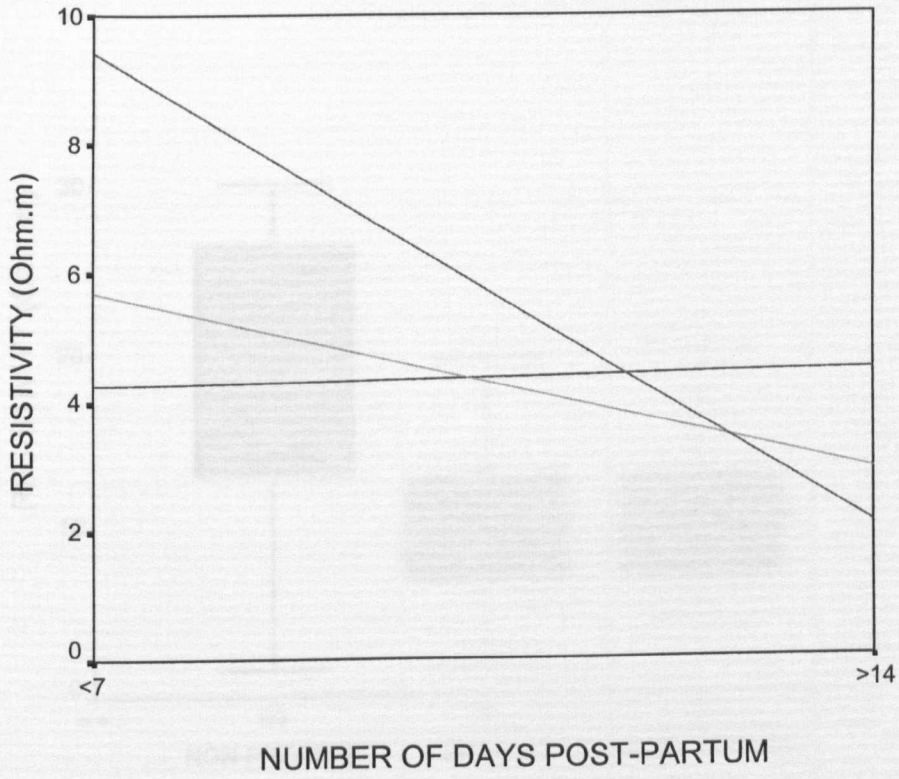

Figure 6.2 Resistivity plotted against number of days post-partum for the 3 patients who had sequential readings, using the 8mm probe. Each line represents an individual patient.

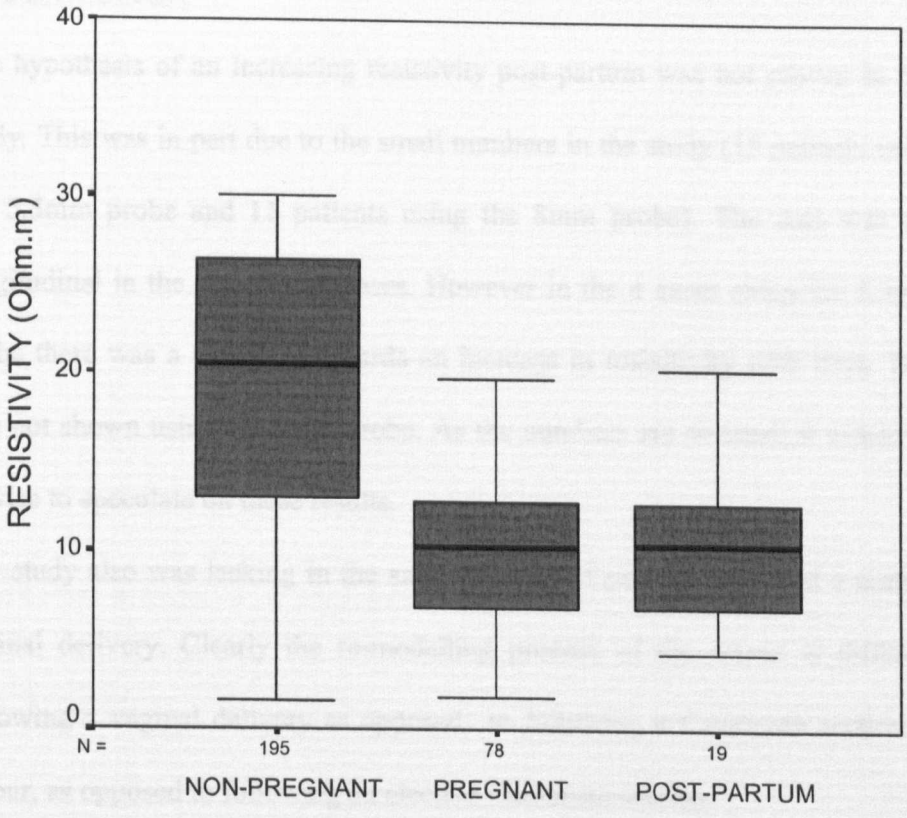

Figure 6.3 Comparison of mean (interquartile range) resistivity in the non-pregnant, pregnant and post-partum patients using the 5.5mm probe.

6.4 DISCUSSION

The hypothesis of an increasing resistivity post-partum was not proven in this study. This was in part due to the small numbers in the study (15 patients using the 5.5mm probe and 11 patients using the 8mm probe). The data was not longitudinal in the majority of cases. However in the 4 cases using the 5.5mm probe there was a tendency towards an increase in resisitivity with time. This was not shown using the 8mm probe. As the numbers are so small it would be unwise to speculate on these results.

The study also was lacking in the small number of patients who had a normal vaginal delivery. Clearly the re-modelling process of the cervix is different following a vaginal delivery as opposed to following a Caesarean section in labour, as opposed to following an elective Caesarean section.

As only 4 patients in the 5.5mm probe section and 3 patients in the 8mm probe section were > two weeks post-partum, it is not surprising that we failed to demonstrate an increase in resistivity.

The comparison of resistivity measurements between the non-pregnant, pregnant, and post-partum patients was limited by the small number of readings in patients beyond fourteen days post-partum.

Clearly longitudinal data specifically investigating the post-partum cervix and the effects of the re-modelling process on electrical impedance measurements is required.

CHAPTER 7 PATIENT ACCEPTABILITY STUDY

7.1 INTRODUCTION

The attitude of patients to a procedure be it in the research setting or indeed the clinical setting is paramount to the potential application of that procedure. In order to assess patients attitude to electrical impedance measurements, we randomley requested patients to fill out a simple questionnaire (Appendix 5).

7.2 PATIENTS AND METHODS

The patients (n=47) were taken from each of the study groups, induction of labour study, longitudinal study, and post-natal study. In the case of the induction of labour and the longitudinal study groups, some women filled in the questionnaire after their first set of readings whilst others filled it in after two or more sets of readings. The post-natal patients filled it in either immediately post natally or at their 6 week visit. This group was recruited regardless of their obstetric outcome.

Patients were asked to complete the questionnaire which consisted of seven questions. The first four compared the comfort and embarrassment associated with the test, compared to their experience with both vaginal examination and cervical smear testing. Two patients were excluded at this stage as they had never had a cervical smear test. The remaining three questions related to whether patients would have the test again, whether the information they received prior to the test was deemed adequate and finally whether they found the test reassuring.

The questionnaires were anonymous and as a consequence it was not possible to analyse the data with respect to the study group to which the patient belonged. To avoid potential patient bias in answering the questions the answers were framed in a different

order e.g. question one's answers were
a) more embarrassing
b) as embarrassing
c) less embarrassing

with question three's order being
a) less embarrassing
b) more embarrassing
c) as embarrassing.

7.3 RESULTS AND DISCUSSION

The results are presented in the same order as the questions were asked on the quetionnaire.

7.3.1. Embarrassment

In order to assess the embarrassment factor we asked patients if they found the test as embarrassing, less embarrassing or more embarrassing as having a vaginal examination or having a cervical smear. The results are shown in Figure 7.1.

It is clear from figure 7.1 that the majority of women found the test as or less embarrassing as having either a vaginal examination or a smear test. This result may be biased as all the examinations were performed by the same male examiner and by the fact that in some cases the patients were being seen on a weekly basis for their antenatal care by the same person.

7.3.2 Comfort

This question again compared the test to a vaginal examination or a smear test. As the majority of women find these examinations uncomfortable the question was deliberately phrased in the negative. The results are shown in figure 7.2. 60% of women found the test as uncomfortable as either of the two other types of internal examination. The remainder found it less uncomfortable, indicating the acceptability of the test. However one patient found it more uncomfortable.

7.3.3 Would you have the test again if it were part of your care package?

If the test is to assume a role in clinical practice then it is almost certain that serial measurements will need to be obtained. If the test is unacceptable to women then the default rate will be unacceptably high. It is thus reassuring that 91% of women would undergo retesting.

7.3.4 Information given prior to testing

This question was designed to assess if the amount of both verbal and written information given to the woman prior to undergoing the test was sufficient. 97.8% felt that it was about right with only one woman saying that she would have liked more information.

7.3.5 Effect of the test

Here we attempted to assess the effect of having the test on the woman. In a clinical research setting it is imperative that participating in the study has no detrimental effect on the woman or indeed the pregnancy itself. Figure 7.3 clearly demonstrates that the majority

of women that participated in the study were reassured that their participation had no detrimental effect on them.

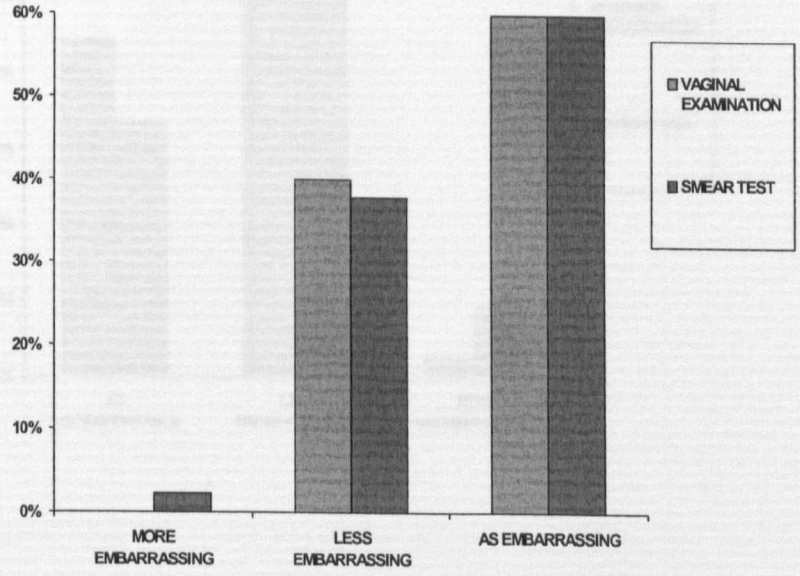

Figure 7.1 Patient embarrassment factor in having the test.

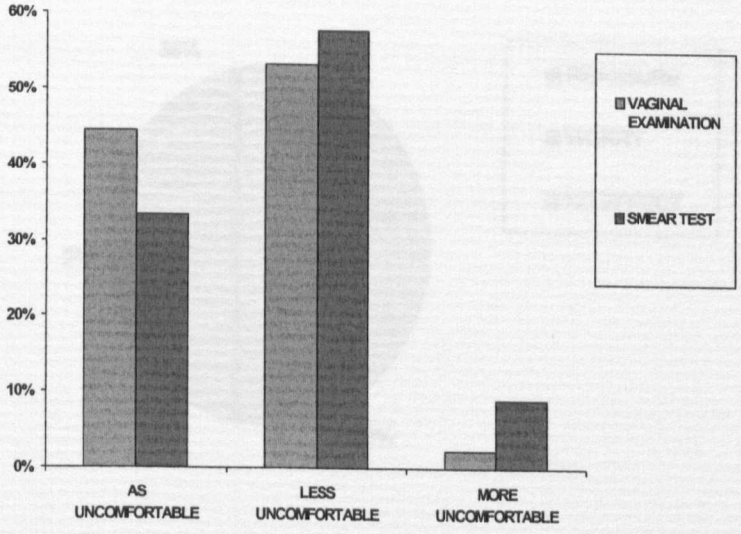

Figure 7.2 Patient comfort factor in having the test.

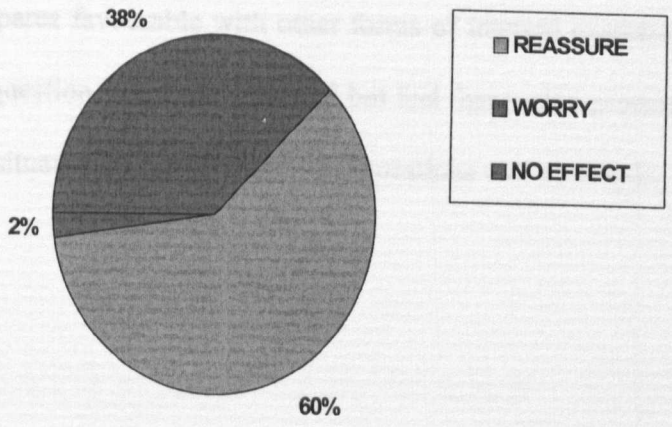

Figure 7.3 Effect of the test on the patients pregnancy.

7.4 CONCLUSION

The questionnaire indicates a high patient satisfaction with the test and compares favourable with other forms of internal examination. We accept that the questions were not validated but feel that such a process was not required in this situation as the content of the questions was so simple.

CHAPTER 8 SUMMARY AND FUTURE WORK

8.1 SUMMARY

This is the first time that electrical impedance studies have been performed on the pregnant cervix.

In this thesis the following has been demonstrated;

1. An inter-observer variability in resistivity readings, initially of the order of 20%, but decreasing to 1% once proficiency with the technique was established.

2. An intra-observer variability in resistivity readings of less than 15% in 94% of cases using the 5.5mm probe and 90% when using the 8mm probe.

3. A degree of heterogeneity in the pregnant cervix as attested to by the differences in resistivity measurements on different sites on the cervix. Some of these changes were partly due to technical difficulties. Nevertheless there appeared to be an increase in extracellular resistivity measurements between the anterior and posterior lips of the external cervical os.

4. A positive correlation between the resistivity measurements and gestational age using the 5.5mm probe. No significant correlations were identified between resistivity readings and both parity and maternal age.

5. A statistically significant difference in resistivity readings when comparing the non-pregnant and pregnant cervix. The change in readings was in a direction which reflected the increase in tissue hydration described by others.

6. A statistically significant difference between readings for ripe and unripe cervices at the time of induction of labour, with a fall in extracellular resistivity with increasing favourability as assessed by the Bishop score. This was accompanied by an increase in intracellular resistivity with increasing cervical favourability.

The effect of prostaglandin administration on the pregnant cervix demonstrated a decrease in extracellular resistivity and an increase in intracellular resistivity associated with the cervical ripening process. Whilst the results were neither of statistical nor of clinical significance, they were nevertheless in the direction predicted.

7. A statistically significant correlation between extracellular resistivity and interval to delivery using the 8mm probe.

8. A new investigative modality that had high patient acceptability.

To date the findings demonstrated in this thesis conceptually agree with the literature on the pregnant cervix. Thus it is imperative to continue with further studies of this new investigative modality.

8.2 SUGGESTED FUTURE WORK

Future methodological studies would need to address the effect of the pressure applied by the probe to the cervix. This would require a simple pressure measuring device to be attached to the probe. A larger inter-observer study using more investigators needs to clarify if our findings are reproducible, particularly if this investigation is to gain use In the clinical setting. Our studies are not large enough to determine whether the cervix is a homogenous or heterogeneous structure and so further studies are required to assess the importance of taking measurements from different sites on the cervix.

In these studies much of the longitudinal data was either obtained from measurements made close to term or in a cohort of patients with a number of previous preterm deliveries. A longitudinal study of low risk and so potentially

normal pregnancies is required. This would have the advantage of firstly characterising the cervix throughout pregnancy and secondly retrospectively ascribing risk to the pregnancy based on the resistivity readings. Such a study could then lead to a prospective randomised intervention study based on resistivity readings.

It is uncertain if the cervix has been measured at the depth at which true cervical change is occurring prior to the onset of labour. A future study would be required using a distant electrode, which would enable us to measure at a greater depth of penetration. A system has been devised and a comparative study of the results presented in this thesis is currently underway.

The accurate determination of patients in threatened idiopathic preterm labour who subsequently deliver has so far eluded us. A comparative study of the resistivity readings of those that deliver *versus* those who settle is required.

The effects of other induction agents on the cervix and resistivity readings also deserves investigation.

It is clear that the results presented in this thesis are preliminary results as this was the first time that such studies were undertaken. The results in the main, can be explained by our understanding, albeit incomplete, of the physiological changes seen in the pregnant cervix.

The findings are encouraging and we believe warrant further study.

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APPENDICES

APPENDIX 1

Patient information sheet and consent for induction of labour study

Dear

You are about to have an induction of labour which your consultant has requested. Induction of labour can sometimes proceed very easily and occasionally can be quite difficult.

When you come into hospital, we will perform a vaginal examination to assess the cervix (neck of the womb). If the neck of the womb is soft and open, then the induction has a greater chance of being successful. If the neck of the womb is closed and hard then the induction has a greater chance of failing. The tablets we put into the vagina have the effect of making a hard closed cervix into a soft open one.

We are looking at a new method of assessing the cervix using a small instrument which, when touched onto the neck of the womb, can tell us the degree of hardness by looking at electrical characteristics of the cervix.

This new method is called electrical impedance and we would be grateful if you would let us perform an electrical impedance study at the same time as you have your vaginal examination to feel the cervix.

It is possible that the electrical impedance studies will give us a better idea of the softness of the cervix and therefore we would be in a better position to counsel patients in the future about their chances of a successful induction

The electrical impedance studies will not affect the health of you or your baby and merely involves touching the cervix with the electrical impedance probe.

We would like your help with this study as in the long term it may help us provide a better service in then future. Thank you for your kind consideration.

Yours sincerely

DR M P O'CONNELL **MR S W LINDOW**

CONSENT FOR CLINICAL INVESTIGATION

I, the undersigned----------Hospital No.----------

hereby declare that the nature, purpose and possible consequences of the proposed investigation and treatment regarding ----------

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including the procedure of ----------have been fully explained to me by Dr----------and that I understand the explanation. I am aware that some aspects of the investigation and treatment may be of a research nature. Having been assured that I will not be exposed to any unreasonable or unwarranted risk, I agree to participate voluntarily in the proposed investigation. I may refuse consent without influencing my care or manner of delivery. I may withdraw consent at any time without prejudice to my care.

SIGNATURE OF THE PATIENT:----------

SIGNATURE OF THE DOCTOR:----------

DATE:----------

APPENDIX 2

Patient information sheet and consent for cervical assessment study

Dear

We are conducting a study to look at a new method of assessing the cervix (neck of the womb). The neck of the womb opens before labour begins and we feel that the assessment of the neck of the womb may identify women who are due to give birth early (preterm birth is one of the biggest problems that we face in the care of pregnant women).

We would be grateful for your help if we could perform a gentle vaginal examination, something similar to having a smear test, and touching the neck of the womb with a small instrument. This will not cause any bleeding and will be no more than a little uncomfortable.

It is by examining women who are in a normal pregnancy like yourself that we can try and identify women who may face problems.

We would be grateful for your help with this study and please be assured that your privacy will be respected. It is however, a study which could prove to be of great worth to pregnant women in the future.

Thank you for your help

DR M P O'CONNELL **MR S W LINDOW**

CONSENT FOR CLINICAL INVESTIGATION

I, the undersigned----------Hospital No.----------

hereby declare that the nature, purpose and possible consequences of the proposed investigation and treatment regarding ----------

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SIGNATURE OF THE PATIENT:----------

SIGNATURE OF THE DOCTOR:----------

DATE:----------

APPENDIX 3
Patient information sheet and consent for post-partum study

Congratulations on the birth of your baby.

Although you have delivered a healthy baby at term, there would be some women who are unfortunate to deliver a preterm baby which may have significant problems.

We are trying to develop a method of establishing whether or not a women is likely to deliver prematurely or not in order that we can try and prevent this premature (early) birth.

We would be grateful if you could perhaps allow us to study your cervix (neck of the womb) for three days following your delivery.

This would involve a gentle speculum examination to allow us to examine your cervix with a small instrument.

This would not cause you any pain and we have deliberately excluded women who have had episotomies or tears which would be obviously be painful.

Although we realise this would be slightly inconvenient, we would be very grateful for your help as the information that we find out may allow us to give a better service to women in the future.

It is by women like yourselves helping us that we can try to ensure that all women in the future have a healthy baby like yourself.

Thank you for your kind co-operation

Yours sincerely

DR M P O'CONNELL **MR S W LINDOW**

CONSENT FOR CLINICAL INVESTIGATION

I, the undersigned----------Hospital No.----------

hereby declare that the nature, purpose and possible consequences of the proposed investigation and treatment regarding ----------

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including the procedure of ----------have been fully explained to me by Dr----------and that I understand the explanation. I am aware that some aspects of the investigation and treatment may be of a research nature. Having been assured that I will not be exposed to any unreasonable or unwarranted risk, I agree to participate voluntarily in the proposed investigation. I may refuse consent without influencing my care or manner of delivery. I may withdraw consent at any time without prejudice to my care.

SIGNATURE OF THE PATIENT:----------

SIGNATURE OF THE DOCTOR:----------

DATE:----------

APPENDIX 4

Protocol for insertion of prostin pessaries for induction of labour

(Hull Maternity Hospital, Royal Hull Hospitals)

Registered Midwives may insert prostin pessaries (on standing orders) for the purpose of inducing labour, providing that the indication has been agreed by an obstetrician, and there are no contra-indications.

The exception will be: Women who have had a previous Caesarean section

Women who have spontaneous ruptured membranes

In the above case, midwives may still administer prostin pessaries, but prior to insertion, they must be individually prescribed by a medical practitioner on a drug administration chart.

The position, effacement, and dilatation of the cervix should be assessed prior to the insertion of a prostin pessary in the posterior vaginal fornix.

All women with intra-uterine growth retardation, evidence of placental insufficiency or asthmatics should be given an initial dose of prostin pessary 3mgs. These women should ideally be admitted in the morning.

Primigravida (All am admissions)

Prostin pessary 3mgs, repeat 6 hours later, if needed. Leave overnight then either artificial rupture of the membranes (ARM) or repeat prostin pessary 3mgs with a further prostin 3mgs in 6 hours if required.

Primigravida (All pm admissions)

Normally Prostin pessary 6mgs, however after vaginal examination, a smaller dose may be indicated, e.g. a particularly favourable cervix, in which a lesser dose will be used. The following morning ARM or prostin pessary 3mgs. Repeat prostin pessary 3mgs, after 6 hours, if required, then assess the following morning.

Multigravida (am or pm admissions)

Prostin pessary 3mgs. Repeat after 6 hours if required.

Total dose of prostin

Primigravida - 12 mgs Multigravida - 6mgs.

Following the above the cervix is assessed by an experienced person. A further dose of prostin can only be administered after consultation with a Consultant or Senior registrar.

Before inserting a prostin pessary the fetal heart rate should be monitored on CTG for 20-30 minutes. If the trace is normal proceed with the induction. If the trace is abnormal, refer to an obstetrician.

The fetal heart rate should be monitored on CTG for one hour after insertion of the prostin pessary.

High risk cases - repeat fetal heart tracing for 30 minutes every 3-4 hours.

In all cases, when uterine contractions commence, fetal monitoring should be carried out for 30 minutes, with additional monitoring if indicated.

If prostin is required to be administered in any other way it should be written in the casenotes by the Consultant Obstetrician.

January 1997 Review January 1999.

APPENDIX 5

Questionnaire

We would greatly appreciate it if you would take a few minutes to complete the following questionnaire.

Please circle the answer that most applies to your experience of this test.

1. In comparison to having a vaginal examination was the test;

a) more embarrassing

b) as embarrassing

c) less embarrassing

2. In comparison to having a vaginal examination was the test;

a) as uncomfortable

b) less uncomfortable

c) more uncomfortable

3. In comparison to having a smear test was the test;

a) less embarrassing

b) more embarrassing

c) as embarrassing

4. In comparison to having a smear test was the test;

a) more uncomfortable

b) as uncomfortable

c) less uncomfortable

5. Would have the test again if it was part of your care package;

a) yes

b) no

c) maybe

6.Was the information you received about the test

a) Too much

b) Too little

c) About right

7. Do tests like this one in pregnancy

a) reassure you

b) worry you

c) have no effect

Many thanks for helping us with our research study into the cervix (neck of the womb) in pregnancy.

Dr. M. P. O'Connell
Clinical Research Fellow