OUTI PALOMÄKI

Treatment of Labour Contractions and Pain

Effects on Foetal Well-being and Uterine Contractility Monitored by Cardiotocography

■

ACADEMIC DISSERTATION

To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the main auditorium of Building K,
Medical School of the University of Tampere,
Teiskontie 35, Tampere, on September 30th, 2005, at 12 o'clock.

Acta Universitatis Tamperensis 1104

ACADEMIC DISSERTATION

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www.uta.fi/taju
http://granum.uta.fi

Cover design by
Juha Siro

Printed dissertation
Acta Universitatis Tamperensis 1104
ISBN 951-44-6407-9
ISSN 1455-1616

Electronic dissertation
Acta Electronica Universitatis Tamperensis 468
ISBN 951-44-6408-7
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2005

To Markku, Taija and Tinja

1 ABSTRACT

The aim of this study was to evaluate the applicability and safety of some medical treatments of labour contractions and pain. Special interest was focused on the effects of various kinds of medication on foetal well-being, monitored by cardiotocography (CTG), progress of labour and neonatal outcome. In addition, the reliability of CTG as a tool to assess foetal condition during labour and delivery was studied. The kinds of medication that affect uterine contractility via β-receptors in specific labour disorders (dystocia and foetal distress) were evaluated. The applicability, safety and effectiveness of paracervical block as an alternative pain relief method in the first stage of labour were studied. Inter-observer agreement in interpretation of intrapartum CTG readings and obstetricians' recommendations for intervention based on CTG data were also evaluated.

The study population consisted of 617 parturients giving birth at Tampere University Hospital between years 2001 and 2004, and 31 specialist and resident obstetricians assessing 22 intrapartum CTG readings.

In the randomised, double-blind study, the β-blocking agent propranolol combined with oxytocin versus placebo plus oxytocin, in the treatment of arrested labour (dystocia) was studied. There was no difference between the groups in the rate of Caesarean sections but the percentage proportion of the augmented part of labour was significantly shorter with propranolol. Propranolol did not affect foetal CTG pathology, and there were no neonatal side-effects. Propranolol can be used as an additional form of medication in arrested labour.

After recognition of severe CTG abnormality in the first stage of labour, and then using a β-mimetic agent (ritodrine hydrochloride or bufenine hydrochloride), in 67% of cases the CTG pattern normalized at a mean of 4 minutes after the beginning of intravenous tocolysis in the retrospective study. No characteristic feature of the parturient, labour course or CTG abnormality, nor the parameters of uterine contractile activity were found to be predictive factors as regards the effect of tocolysis on CTG. No adverse effects of tocolytic therapy were found. Tocolysis with a β-mimetic agent is an effective method to normalize the CTG pattern during the first stage of labour, even in cases without uterine hypertonicity.

In the randomised, double-blind study, paracervical block (PCB) with levobupivacaine and racemic bupivacaine were compared by means of CTG pathology. No significant differences were found between the drugs in safety or effectiveness. The incidence of any pathological result in CTG was 10.4% in the levobupivacaine group and 12.8% in the racemic bupivacaine group. The incidence of foetal bradycardia in the groups was 2.6% and 3.8% respectively. All the CTG changes were transient, and no operative intervention was indicated in CTG. No difference in analgesic effect between the drugs was found. Most of the parturients in the levobupivacaine group (97%) and in the racemic bupivacaine group (96%) had spontaneous vaginal delivery. Neonatal outcome was good in both groups. The best pain relief after PCB was achieved among primiparas. Good pain relief was connected with a high pain score before PCB, and an experienced obstetrician performing the PCB.

In an inquiry form study 31 obstetricians interpreted intrapartum CTG readings from 22 parturients. Inter-observer agreement in CTG interpretation and decision-making was assessed by means of proportions of agreement (Pa) with 95% confidence intervals (CIs). Inter-observer variation as regards abnormal CTG readings, and recommendations for intervention, was found to be wide. To improve the reliability of CTG, uniform classification and standardized training in CTG interpretation are needed, as well as increased use of computerized CTG.

2 TIIVISTELMÄ

Väitöskirjatutkimuksen tarkoituksena oli tutkia eräiden kohdun supistuksiin ja synnytyskipuun vaikuttavien lääkkeiden käyttökelpoisuutta ja turvallisuutta. Erityisesti kiinnostuksen kohteena oli tutkittujen lääkitysten vaikutus sikiön sykekäyrään, synnytyksen kulkuun ja vastasyntyneen ennusteeseen. Tutkimuksessa paneuduttiin β-reseptoreiden kautta tapahtuvaan kohdun supistustoiminnan säätelyyn tietyissä synnytykseen liittyvissä häiriötiloissa. Näitä häiriötiloja olivat toisaalta edistymättömyys kohdun heikkoon supistustoimintaan liittyen ja toisaalta sikiön synnytyksenaikainen ahdinkotila, joka oli todettu sykekäyrämuutosten perusteella. Toisena tutkimusosa-alueena oli kohdunkaulapuudutuksen käyttömahdollisuus, turvallisuus ja teho vaihtoehtoisena synnytyskivun lievitysmenetelmänä synnytyksen avautumisvaiheessa. Näiden supistuksiin ja kivunhoitoon liittyvien tutkimuskohteiden lisäksi paneuduttiin sikiön sykekäyrän tulkintaan ja tulkintaeroavaisuuksiin hoitavien synnytyslääkäreiden välillä.

Tutkimukseen osallistui yhteensä 617 synnyttäjää Tampereen yliopistollisesta sairaalasta. Lisäksi 31 synnytyslääkäriä tulkitsi 22:a synnytyksenaikaista sykekäyrää ja antoi hoitosuosituksensa käyrän perusteella.

Ensimmäisessä osatyössä, joka oli satunnaistettu lumekontrolloitu kaksoissokkotutkimus, verrattiin β-salpaaja propranololin ja oksitosiinin yhdistelmähoitoa ja pelkkää oksitosiinia pysähtyneen synnytyksen avautumisvaiheen hoidossa. Tutkimuksessa todettiin, että propranololin liittäminen yleisesti käytetyn oksitosiinin rinnalle ei vaikuttanut keisarileikkaukseen päätyneiden synnytysten määrään, mutta lyhensi lääkityksen aloittamisesta syntymään kulunutta aikaa. Propranololin käyttöön ei liittynyt sykekäyräpatologiaa ja sen todettiin olevan turvallinen hoito vastasyntyneille, ja näinollen sitä voidaan käyttää oksitosiinin lisäksi lääkityksenä hoidettaessa pysähtynyttä synnytyksen avautumisvaihetta.

Toinen, retrospektiivinen osatyö käsitteli vakavien synnytyksen avautumisvaiheen aikaisten sykekäyrämuutosten hoitoa β-mimeettisellä lääkeaineella (ritodriinilla tai bufeninilla). Vaikean sykekäyräpatologian toteamisen jälkeen β-mimeettistä lääkehoitoa saaneilla potilailla 67%:lla sykekäyrä normaalistui lääkkeen annon jälkeen keskimäärin neljässä minuutissa. Tutkimuksessa todettiin myös, ettei ole mahdollista löytää synnyttäjään, synnytykseen, sykekäyrämuutoksen tyyppiin tai supistusten laatuun liittyviä erityispiirteitä, joiden perusteella tämän hoidon tehoa voitaisiin ennustaa.

Hoitoon ei liittynyt sivuvaikutuksia. β-mimeettisen lääkehoidon todettiin olevan tehokas ja turvallinen hoitomuoto, joten sitä voidaan suositella vaikean sykekäyräpatologian hoitoon myös potilailla, joilla muutoksiin ei liity kohdun liiallista supistustoimintaa.

Kolmas osatyö oli satunnaistettu kaksoissokkotutkimus, jossa verrattiin sykekäyrämuutoksia kahdella puuduteaineella, levobupivakaiinilla ja raseemisella bupivakaiinilla annettujen kohdunkaulapuudutusten jälkeen. Puuduteaineiden välillä ei todettu eroa turvallisuudessa eikä tehossa. Poikkeavien sykekäyrälöydösten määrä oli 10.4% levobupivakaiinilla suoritetun puudutuksen jälkeen ja 12.8% raseemisen bupivakaiinin ryhmässä. Vastaavasti sikiön sykehidastumaa esiintyi puudutuksen jälkeen 2.6%:lla levobupivakaiiniryhmässä ja 3.8%:lla raseemisen bupivakaiinin ryhmässä. Kaikki sykekäyrämuutokset olivat ohimeneviä, ja yhdellekään synnyttäjälle ei jouduttu tekemään päästävää alatieoperaatiota tai keisarileikkausta sykekäyrämuutosten takia. 97% levobupivakaiiniryhmästä ja 96% raseemisen bupivakaiiniin ryhmästä synnytti säännöllisesti alateitse. Vastasyntyneiden kunto oli hyvä molemmissa ryhmissä.

Neljännessä osatyössä käsiteltiin kohdunkaulapuudutuksen tehoa. Puudutuksen todettiin olevan tehokkain ensisynnyttäjille ja niille synnyttäjille, jotka arvioivat kipunsa kovaksi ennen puudutuksen antamista. Lisäksi erikoislääkärien puuduttamat synnyttäjät puutuivat paremmin kuin erikoistuvien lääkärien puuduttamat.

Viidennessä osatyössä tutkittiin kyselykaavakkeen avulla 31:ltä synnytyslääkäriltä heidän tulkintojaan 22:sta synnytyksenaikaisesta sykekäyrästä sekä heidän hoitosuosituksiaan sykekäyrän perusteella. Tutkimuksessa todettiin, että lääkäreiden tulkinnat olivat yksimielisempiä koskien normaaleja käyriä ja tilanteita, joissa synnytykseen puuttumista ei suositeltu. Tapauksissa, joissa käyrä tulkittiin poikkeavaksi tai suositeltiin operaatiota tai sikiön voinnin varmistamista mikroverinäyttein, tulkitsijoiden väliset erot olivat suurempia. Sykekäyrän tulkintaan liittyvän yhdenmukaisuuden lisäämiseksi on suositeltavaa luoda ja käyttää yhdenmukaista luokittelua ja termistöä sekä jatkuvaa tulkintojen yhdenmukaistamiseen pyrkivää koulutusta. Myös tietokoneavusteisten sykekäyrärekisteröinnin enenevä käyttö on tämän tutkimuksen valossa suositeltavaa.

3 CONTENTS

4 LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I Palomäki O, Uotila J, Tammela O, Kaila T, Lavapuro M, Huhtala H, Tuimala R: A double blind, randomized trial on augmentation of labour with a combination of intravenous propranolol and oxytocin versus oxytocin only. Eur J Obst Gyn Reprod Biol, in press.

II Palomäki O, Jansson M, Huhtala H, Kirkinen P (2004): Severe cardiotocographic pathology at labor: effect of acute intravenous tocolysis. Am J Perinatol 21(6):347-53.

III Palomäki O, Huhtala H, Kirkinen P: A comparative study of the safety of 0.25% levobupivacaine and 0.25% racemic bupivacaine for paracervical block in the first stage of labour. Acta Obstet Gynecol Scand, in press.

IV Palomäki O, Huhtala H, Kirkinen P: What determines the analgesic effect of paracervical block? Acta Obstet Gynecol Scand, in press.

V Palomäki O, Luukkaala T, Luoto R, Tuimala R: Intrapartum cardiotocography – the dilemma of interpretational variation. Submitted.

The publishers of the original communications have kindly given permission to reproduce the articles in this thesis.

5 ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
BE	base excess
bpm	beats per minute
CI	Confidence Interval
CS	Caesarean Section
CTG	Cardiotocography/Cardiotocographic
cGMP	cyclic Guanosine Monophosphate
ECG	Electrocardiography
FHR	Foetal Heart Rate
FIGO	International Federation of Gynaecology & Obstetrics
IU	International Unit
MAP	Mean Arterial Pressure
NICU	Neonatal Intensive Care Unit
NO	Nitric Oxide
OR	Odds Ratio
PCB	Paracervical Block
PI	Pulsatility Index
RI	Resistance Index
SD	Standard Deviation
VAS	Visual Analogue Scale

6 INTRODUCTION

The active phase of first stage of labour is characterizised by regular uterine contractions leading to cervical dilatation. The fetal well-being during contractions is in modern obstetrics monitored by cardiotocography (FIGO 1997, Low et al. 1999, Hadar et al. 2001, Sameshima et al. 2004), computer-based fetal electrocardigraphy (Luzietti et al. 1999, Amer-Wåhlin et al. 2001, Noren et al. 2003, Rosen et al. 2004), pulse oximetry (Penning and Garite 1999, Puertas et al. 2004) or fetal scalp blood samples (Low et al. 1997). After delivery, markers such as the Apgar score, and umbilical blood sample tests define neonatal outcome (Sykes et al. 1982, Ruth and Raivio 1988, Ingemarsson et al. 1997). Excluding cases of chronic or acute diseases, medical treatment during labour is mainly concentrated on the treatment of contractions or labour pain. In cases of hypocontractility the power of contractions can in many cases be strengthened by means of medication. In cases of imminent asphyxia, tocolytic therapy to diminish the contractions is sometimes needed.

Labour pain can be treated by means of non-pharmacological methods such as continuous labour support, baths, touch and massage, maternal movement and positioning, or intradermal water blocks, nitrous oxide, parenteral opioids, paracervical, epidural, spinal or combined anaesthesia (Caton et al. 2002).

The content of this thesis is directed to medical treatment of contractions with β-mimetic and β-blocking agents and treatment of pain by means of paracervical block. Special attention is paid to the effect of these treatments on foetal and neonatal well-being, and cardiotocography as a monitoring tool.

7 REVIEW OF THE LITERATURE

7.1 Definitions

Table 1 shows the definitions used in this thesis.

Table 1 *Definitions*

First stage of labour	From the onset of regular uterine contractions to full dilatation of the cervix (Friedman 1955)
Latent phase of the first stage of labour	From the onset of regular uterine contractions to the point at which the rate of dilatation begins to change (Friedman 1955)
Active phase of the first stage of labour	Acceleration phase, phase of maximal slope and deceleration phase of labour (Friedman 1955)
Cervicograph /Cervimetry	A graphic representation of cervical dilatation as a function of time (Philpott and Castle 1972a)
Hypoxia	Decreased level of oxygen in tissue (ACOG 1995)
Asphyxia	Hypoxia with metabolic acidosis (ACOG 1995)
Fetal stress	A potentially pre-pathological situation manifested by CTG changes, where fetal homeostasis has not been significantly affected (Cibils 1996)
Fetal distress	Pathological alteration of the internal milieu of the foetus (Cibils 1996)

7.2 Uterine contractility during the first stage of labour

7.2.1 Uncomplicated first stage of labour

Human uterus has spontaneous contractility during the whole pregnancy. The uterine activity increases gradually until beginning of labour. During labour, uterine activity increases until delivery (Caldeyro-Barcia and Poseiro 1959).

The first stage of labour is divided into two phases: latent phase and active phase. The latent phase begins when the contractions are regular and painful. In the latent phase the cervix dilates up to 3-4 centimeters (cm) and shortens to less than 0.5 cm of length (Martin and Hutchon 2004).

Initiation of the active phase of labour is defined either by cervical dilatation of 4 cm (Albers 1999) or by the beginning of the phase of maximum slope of a curve that shows cervical dilatation per unit time (see Figure 1) (Friedman 1955, Friedman 1971, Friedman 1996). In the active phase regular uterine contractions become increasingly powerful and frequent and lead to cervical dilatation of 10 cm (Caldeyro-Barcia and Poseiro 1960, Friedman 1971, Martin and Hutchon 2004). According to Friedman's (1955, 1956) studies the length of the active phase of the first stage in nulliparous parturients is 4.9 hours (SD 3.4 hours) and in multiparous parturients 2.2 hours (SD 1.5 hours). As a consequence of different definitions of initiation of the active phase, other investigators have found longer lengths for the active first stage – up to 5.5–7.7 hours for primiparas and 4.4–5.6 hours for multiparas. There are also ethnic differences in the length of labour (Friedman 1996, Albers 1999, Zhang et al. 2002, Jones and Larson 2003). Cervical effacement at the beginning of labour affects the total uterine work during labour and the length of the first stage of labour (Burnhill et al. 1962, Friedman 1996).

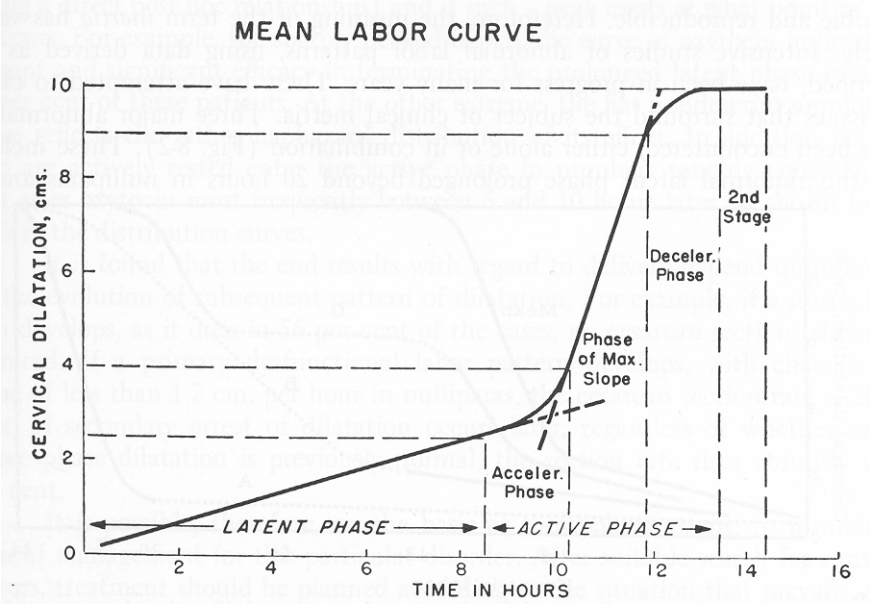


Figure 1 *Friedman's curve: Characteristic sigmoid curve of the function of cervical dilatation versus elapsed time in labour.*
Reprinted from Controversy in Obstetrics and Gynecology, V1(8): 151, Reid and Barton (ed): "Dysfunctional labor," © 1969, with permission from Elsevier.

According to the literature, the power of contractions measured during advanced labour is 100 Montevideo units at the beginning of labour (Caldeyro-Barcia et al. 1957, Caldeyro-Barcia and Poseiro 1959) and between 160 and 300 Montevideo units at a more advanced stage of active phase (Caldeyro-Barcia and Poseiro 1959, Burnhill et al. 1962, Hauth et al. 1986). A frequency of up to 5 contractions in 10 minutes with resultant cervical dilatation is considered an adequate goal for the active phase (ACOG 2003).

7.2.2 Dysfunctional first stage of labour

The first stage of labour is called dysfunctional in cases in which cervical dilatation is delayed or arrested. The classical PPP-triad to reflect the reasons for poor progress of labour is Power, Passage or Passenger (Calder 1999, ACOG 2003). Before diagnosis of insufficient or inappropriate contractions as a reason for dysfunction, disproportion, malpresentation, malposition, foetal macrosomy or maternal anatomical abnormalities have to be excluded.

Arrested labour following labour dysfunction is a leading cause of intrapartum Caesarean section (CS) (O'Driscoll et al. 1984, ACOG 2003). Caesarean section is associated with higher complication and mortality rates than vaginal delivery and risks in the next pregnancies are increased after CS (Hemminki and Meriläinen 1996, Schuitemaker et al. 1997, Jackson and Paterson-Brown 2001, Häger et al. 2004).

Uterine dysfunction can be due to hypotonic contractions: the contractions are weak and infrequent. The contractions can also be incoordinated. In these cases, instead of one pacemaker site in one or other cornu there are separate and independent pacemakers in the uterus, leading to loss of rhythm and coordination of the contractions. Relaxation between contractions can be incomplete, leading to persisting pain and increased intrauterine pressure (Thompson 1969, Greenhill and Friedman 1974).

According to Friedman (1969), three major abnormalities of the first stage of labour are a prolonged latent phase, primary dysfunctional labour and secondary arrest of dilatation (Figure 2). Primary dysfunctional labour is found to occur in about 26% in primiparas and 8% in multiparas (Cardozo and Pearce 1990).

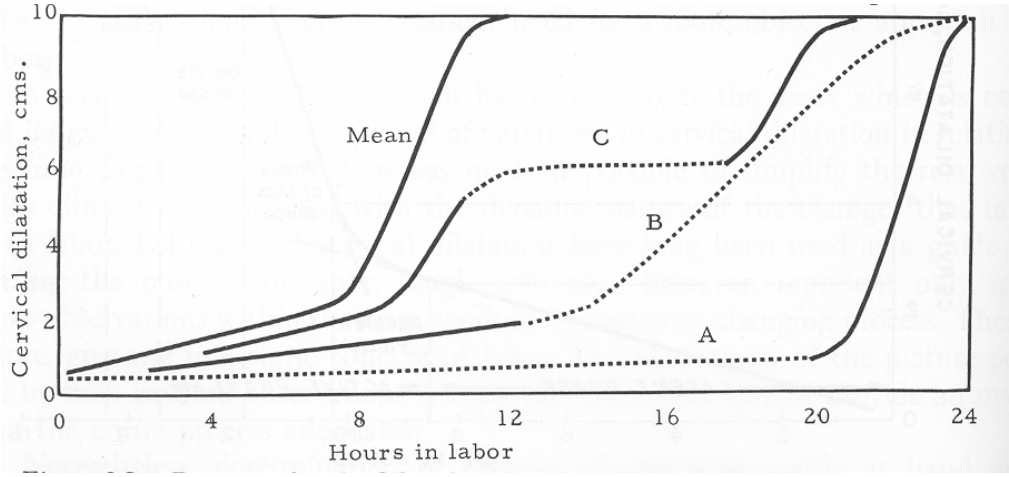


Figure 2 *Three major abnormalities of the first stage of labour according to Friedman: A, prolonged latent phase; B, primary dysfunctional labour; C, secondary arrest of dilatation.*
Reprinted from Controversy in Obstetrics and Gynecology, V1(8): 152, Reid and Barton (ed): "Dysfunctional labor," © 1969, with permission from Elsevier.

Philpott and Castle (1972a, 1972b) created a simple tool to interpret the cervicograph in primiparas and distinguish the parturients whose labour is delayed and in whom active management is needed. They established a set of guidelines based on the cervicograph (see Figure 3). The Alert Line represents a cervical opening rate of 1 cm/hour, which is the mean rate of dilatation of the slowest 10% of primigravidas in the active phase of labour. Crossing this line alerts medical staff to potential problems at an early stage. The Action Line is drawn parallel to the Alert Line but four hours later. Parturients whose labour plots cross the Action Line need further evaluation to exclude foetopelvic disproportion or start labour augmentation with oxytocin.

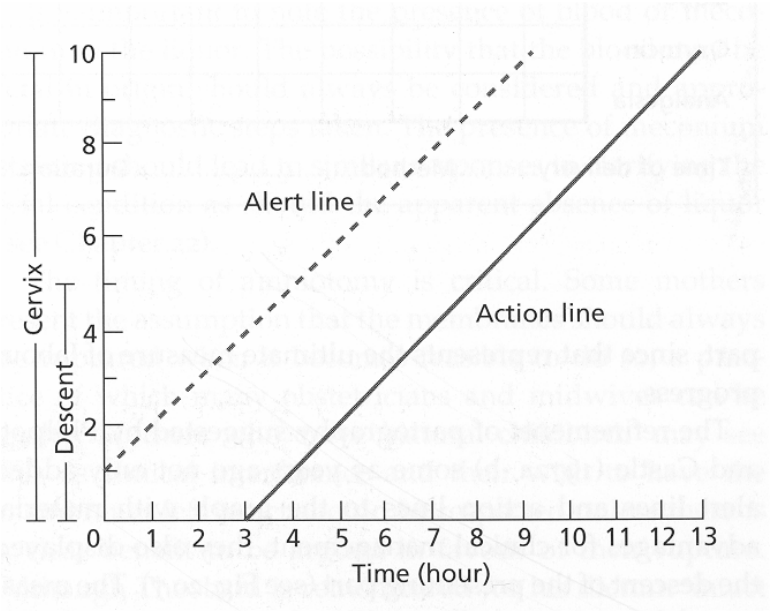


Figure 3 *The cervicograph of Philpott and Castle showing Alert line and Action line. Reprinted from Philpott RH, Castle WM (1972a) Cervicographs in the management of labour in primigravidae. J Obstet Gynaecol Br Commonw 79: 592-598, with permission from Blackwell Publishing.*

Women with failure to progress in the first stage of labour are older, of higher birth order and are likely to have complications such as gestational diabetes, hypertension, premature rupture of membranes, meconium-stained amniotic fluid, polyhydramnion or oligohydramnion, compared with women with non-progressive labour in the second stage (Sheiner et al. 2002). Epidural analgesia and chorioamnionitis have also been associated with slow progress of labour (Satin et al. 1992b, Halpern et al. 1998, Lieberman and O'Donoghue 2002).

7.2.3 Measurement and evaluation of contractions

Measurement of contractions, tocography, is possible by means of external or internal methods. With non-invasive external measurement it is possible to find out the frequency and timing of the contractions, but the method fails to measure the intensity of contractions. Another possibility is intrauterine measurement. In the 1950's and 1960's an abdominal intrauterine catheter was used to study uterine contractility (Alvarez and Caldeyro 1950, Caldeyro-Barcia et al. 1957, Burnhill et al. 1962). In modern obstetrics a cervical intrauterine water-filled or tip-catheter is used (Chia et al. 1995).

The most widely used unit to measure uterine activity is the Montevideo unit. Caldeyro-Barcia *et al.* created it in 1957. The intensity (amplitude) of each contraction is measured by the rise in pressure (mmHg), and the number of contractions per 10 minutes expresses the frequency of contractions. The product

of intensity and frequency (intensity × frequency) is the Montevideo unit (Figure 4).

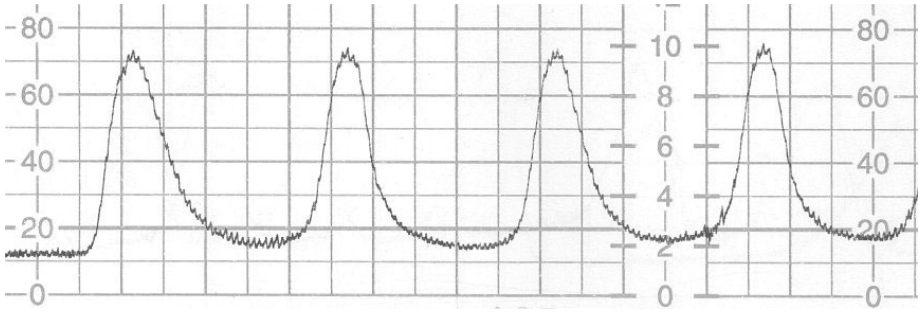


Figure 4 *Counting of Montevideo units: Mean intensity = 55 mmHg, Frequency of contractions 4/10 minutes >> Monteviodeo units = 4×55 = 220.*

Other units and methods to assess uterine activity have also been used. El-Sahwi *et al.* (1967) introduced a new unit for assessment of uterine activity called the Alexandria unit. In the Alexandria unit, a third variant of uterine activity, duration of contraction, is included.

In the 1970's and 1980's computer-based real-time measurements of contractions were developed, but the clinical usefulness of these systems has not been proved. In 1990 Jacobson *et al.* reported that computer-derived contraction assessment was not a better predictor of labour progress than the Montevideo unit, and the correlation of any uterine contractility index with progress of labour was poor (Jacobson et al. 1990).

In order to discover if analysis of the frequency or regularity of uterine contractions could help to distinguish women requiring CS, Oppenheimer *et al.* (2002) calculated the average and standard deviation of five contraction inter-peak times for 30-minute periods. These times were plotted against cervical dilatation. Both average and standard deviation times were found to fall in cases of vaginal delivery, and this phenomenon could not be seen among the women who eventually underwent CS after failure to progress in spite of oxytocin augmentation.

7.3 β-receptors of the human uterus

In 1948 Ahlquist postulated two types of adrenergic receptor, α (alpha) and β (beta). Alpha receptors were found to be excitatory and beta receptors inhibitory. These receptors were found in the uterus in several animals, and also in human uterus (Ahlquist 1948). In 1967 Mahon *et al.* discovered that the inhibitory effect on human uterine motility of the β-agonist isoproterenol could be reversed by the β-adrenergic receptor-blocking drug propranolol. In 1968 Wansbrough *et al.*

found further experimental evidence of the presence of α and β receptors in the human uterus. Alpha receptor blocking agents were found to depress the excitatory response to noradrenaline. The β-blocking agent propranolol prevented the inhibitory response to a β-mimetic agent in pregnant full-term parturients and non-pregnant subjects. Increased uterine activity after propranolol was more marked among non-pregnant women. In 1969 Barden and Stander confirmed the finding that intravenous infusion of propranolol results in significant enhancement of uterine activity in term human pregnancy.

In 1967 the two subgroups of β-receptors, β_1 and β_2, were defined (Lands et al. 1967). The latter predominate in the myometrium, and cardiac β-adrenergic receptors are mostly of the β_1-subtype (Engelhardt et al. 1997).

In 2000 Bardou *et al.* presented the first evidence for the existence of a β_3-receptor subtype in human near-term myometrium. This receptor subtype is under research and may provide a new tool in cases of premature delivery, with fewer vascular adverse effects and less desensitisation during therapy compared with β_2 -blocking agents (Dennedy et al. 2002, Rouget et al. 2004).

7.4 Augmentation of labour

Augmentation of labour means stimulation of uterine contractions when spontaneous contractions do not lead to progressive dilatation of the cervix or descent of the foetus. Augmentation is recommended in cases with less than 3 contractions per 10 minutes, or when the intensity of contractions is less than 25 mmHg above baseline, or both (ACOG 2003). The most widely used methods for labour augmentation are amniotomy and oxytocin infusion. The literature concerning the role of propranolol in labour augmentation is scarce.

7.4.1 Amniotomy

The first step in labour augmentation is amniotomy. Amniotomy has been found to be associated with a reduction in the duration of labour and the use of oxytocin (Garite et al. 1993, Rouse et al. 1994). On the other hand, the risk of chorioamnionitis may be increased (ACOG 2003).

7.4.2 Oxytocin

7.4.2.1 Prophylactic use of oxytocin

In an attempt to resolve the problem of labour dystocia and consequently, high rate of CS in these deliveries, a model called Active Management of Labour was

created in the National Maternity Hospital, Dublin (O'Driscoll et al. 1970, O'Driscoll et al. 1984). Management begins with strict criteria for diagnosis of labour. When the parturient is taken to the labour ward, the progress of labour is measured in terms of dilatation of the cervix. The slowest acceptable rate is 1cm/hour, which allows a maximum of ten hours for full dilatation. Intact membranes are ruptured routinely and one-to-one midwifery care is available for every parturient. In nulliparous women, lack of progress is treated with oxytocin. Intravenous infusion of 6 to 40 mU oxytocin/minute is used, but no more than a total dose of 10 Units of oxytocin is used. The longest period in the labour unit is 12 hours; ten to full dilatation and 2 hours for the second stage of labour. After 12 hours CS is performed unless safe vaginal delivery can be predicted within one hour. With this management O'Driscoll *et al.* (1984) showed a Caesarean section rate of 4.8% and a forceps rate of 6.3%. The CS rate after an indication of dystocia was 1.5% among primiparas and 0.2% among multiparas, and oxytocin was given to 41% of primiparas. Epidural block was available, but the analgesia rate is not mentioned in the paper.

One thousand primiparous labours in the same labour unit were involved in a prospective observational study twenty years after the previous study, with the same methods of active management of labour. In this study the Caesarean section rate was still low, 4.2%, but the incidence of operative vaginal delivery rose to 24% and the epidural analgesia rate to 72%. Oxytocin was used in 51.9% of cases (Bohra et al. 2003).

In a randomised trial of active management of labour Frigoletto *et al.* (1995) found no difference between the active management group and the usual-care group in the rate of CS. A total of 1934 nulliparous parturients were randomised to the two groups. The active management group was treated in a similar way as the parturients in the study by O'Driscoll *et al.* (1984). Labour was shortened by 2.7 hours by active management, and the rate of maternal fever was lower in the active management group. Sadler *et al.* (2000, 2001) reported similar findings in a randomised controlled trial with 651 primiparas: active management did not reduce the CS rate, but did shorten the length of the first stage of labour and reduce the risk of prolonged labour. No difference in neonatal outcome was seen. Satisfaction was high in both groups (77%).

The criticism of active management of labour is that the effect on duration of labour is relatively limited and amniotomy in all and oxytocin in half of the parturients would need extremely good evidence of safety and a proof of the reduction of adverse outcome (Olah and Gee 1996, Thornton 1997).

7.4.2.2 Therapeutic use of oxytocin

Another obstetric practice is to avoid intervention in normal labour and to use oxytocin only in labour abnormalities. In 1990 Cardozo and Pearce compared oxytocin and saline for primary dysfunctional labour or secondary arrest of cervical dilatation in an open randomised trial. Oxytocin was superior to saline in both abnormalities without increasing the CS rate because of foetal distress.

A delay in initiating oxytocin treatment may affect the success rate of vaginal delivery. In a retrospective study by Saunders and Spiby (1990) augmentation within two hours of the first evidence of labour delay was associated with a 10% CS rate, compared with 28% in women treated after a longer interval.

Several regimens have been used in oxytocin augmentation. In a low dose regimen the starting dose is 0.5–2 mU/minute and the increase in dosage is 1–2 mU/min at 15- to 40-minute intervals. In a high dose regimen the initial dose is 4–6 mU/min and the increase in dosage is 4–6 mU/min at 15- to 30-minute intervals. In randomised studies the high dose regimen has been associated with significant shortening of labour and lowering of the CS rate for dystocia without an increase in the incidence of labour or neonatal complications (Satin et al. 1992a, Xenakis et al. 1995, Merrill and Zlatnik 1999).

Rouse *et al.* (2001) criticised the policy of carrying out CS after two hours of the arrest of labour. In their material they found that cases of oxytocin-augmented labour proceed at slower rates than spontaneous labours. Sixty-one per cent of the parturients whose labour arrest was over 2 hours achieved vaginal delivery when oxytocin augmentation was continued up to 4 hours (ACOG 1996, Rouse et al. 1999, Rouse et al. 2001, ACOG 2003).

7.4.3 Prostaglandin E_2

To test the hypothesis that exogenous prostaglandins would be useful in labour augmentation, a randomised, prospective study on prostaglandin E_2 (PgE_2) vaginal gel in the treatment of dystocia was carried out recently. A single 1 mg dose of PgE_2 vaginal gel was found to be more effective than placebo in resolving dystocia (Oppenheimer et al. 2005).

7.4.4 Propranolol

A few studies on the non-selective β-blocking agent propranolol for labour augmentation have been published, the first of them in 1975. Mitrani *et al.* (1975) treated 10 primigravidae with dysfunctional labour with 4 mg of intravenous propranolol. After 2.5–4 hours' labour arrest the average time until spontaneous delivery was 77 minutes after propranolol injection. All newborns were born with good Apgar scores (9 or 10), but transient or relative bradycardia was seen in 5 cases out of ten.

In 1996 a randomised trial of oxytocin alone and with propranolol in the management of dysfunctional labour was published. Ninety-six parturients received randomised augmentation with oxytocin and 2 mg intravenous propranolol, or oxytocin and placebo. The propranolol/placebo dosage was repeated after one hour if the cervix was not dilated after the first dosage. Oxytocin was administered at 1–2 mU/minute and increased by 1–2 mU/min every 30 minutes until a uterine power of 150 Montevideo units was reached. Women who did not respond to the second administration of propranolol/

placebo underwent CS. In this study, the CS rate was significantly reduced in the propranolol group versus the placebo group (26.5% vs. 51.1%). There were no differences in neonatal outcome (Sanchez-Ramos et al. 1996).

Two additional small studies have been published on propranolol use in term parturients. In one preliminary randomised report from Puerto Rico, with 57 primiparas, 2 mg intravenous propranolol was given every 4 hours during labour, and the control group received no medication. Dysfunctional labour was not included; thus propranolol was used for modification of active management of labour in a prophylactic manner. No statistically significant reduction in CS rate was found. The authors considered that statistical significance was not reached because of small sample size and the low CS rate in their population (Adamsons et al. 1999).

Propranolol for labour induction in prolonged pregnancy was studied in 60 parturients in Poland. Favourable induction was found in 88% of cases, and no adverse foetal or maternal effects were found. Propranolol shortened the first stage of labour by approximately 30% (Ziolkowski 1994).

7.4.5 Opiates

Although epidural analgesia is superior as a means of pain relief compared with parenteral opioids (Halpern et al. 1998, Bricker and Lavender 2002), opioids are still widely used for labour analgesia, especially in areas where regional analgesia is not available for all parturients. Parenteral meperidine is a widely used opiate in many Latin American countries. It is thought to increase the power of contractions and has been used in cases of dystocia. In a recent randomised controlled trial with 407 parturients no statistically significant differences between meperidine and placebo groups in length of labour were found. Low Apgar scores, umbilical artery acidosis and admission to neonatal care units were increased in meperidine group. According to the results of this trial, meperidine is not a suitable drug for labour augmentation (Sosa et al. 2004).

7.5 Intrauterine resuscitation

7.5.1 CTG criteria for foetal distress

Foetal distress in the active phase of labour is usually diagnosed by suspicious foetal heart rate (FHR) patterns with or without scalp pH measurement (Thurlow and Kinsella 2002). According to Huddleston (1999), the generally accepted FHR criteria for foetal distress are:

1) Persistent late decelerations, irrespective of deceleration depth or
2) Persistent severe variable decelerations, especially those with slow returns to the FHR baseline or
3) Prolonged decelerations lasting > 2 minutes
4) Depressed variability or reactivity together with any of the above represents a potentially more serious situation

Principally similar criteria with minor variation have been stated and published in recent years (FIGO 1987, ACOG 1995, Dellinger and Boehm 1995, FIGO 1997).

7.5.2 Management of intrauterine resuscitation

Intrauterine resuscitation after diagnosis of foetal distress by means of CTG or scalp pH includes discontinuation of oxytocin, initial left lateral recumbent positioning followed by right lateral or knee-elbow positioning if necessary, maternal oxygen administration, rapid intravenous infusion of non-glucose crystalloid, treatment of hypotension if needed, inhibition of uterine contractions by tocolytic therapy and consideration of amnioinfusion (ACOG 1995, Thurlow and Kinsella 2002).

7.5.3 Tocolytic therapy with β-mimetic drugs

The most commonly used β-adrenergic tocolytic drug is a single dose of terbutaline, 0.25 mg, given intravenously or subcutaneously (Thurlow and Kinsella 2002). Ritodrine, fenoterol and hexoprenaline have also been used in emergency tocolysis. The binding of these drugs to β_2 receptors on the surface of myocytes mediates myometrial relaxation by stimulating cyclic adenosine monophosphate. Cellular calcium balance is altered and myosin light-chain kinase is inhibited (Rodts-Palenik and Morrison 2002).

The first studies on acute tocolysis with β-mimetic agents, for foetal distress, were published in 1969. Tocolysis was found to have a positive effect on CTG readings and the acid-base balance of the foetus (Gamissans et al. 1969, Gamissans et al. 1971).

Several non-controlled studies on β-mimetic tocolysis for pathological CTG readings and/or low pH were carried out in the 1980's. The largest of these

studies involved 553 cases of intrapartum foetal acidosis (scalp pH < 7.25). An improvement of foetal pH greater than 0.05 was found in 72.8% of cases with ritodrine treatment. The recovery rate was the same, independent of the percentage of uterine activity inhibition (Cabero et al. 1988). In another smaller study an emergency CS could be avoided in 83% of cases with CTG pathology (Gummerus 1982). In a few further studies, an improvement in CTG was found in most cases after tocolysis (Ingemarsson et al. 1985, Mendez-Bauer et al. 1987, Shekarloo et al. 1989, Egarter et al. 1990).

In controlled studies, β-mimetics have been superior to oxygen inhalation (Hidaka et al. 1987) and magnesium sulphate (Magann et al. 1993) in correcting foetal heart rate abnormalities.

Further, in a few studies β-mimetics have been compared with standard interventions without tocolysis in treatment of suspected intrapartum foetal distress. In three prospective series an improvement in Apgar scores (Burke et al. 1989), in acid-base status of the foetus (Patriarco et al. 1987) and in foetal heart rate pattern (Kulier et al. 1997) have been found after tocolysis.

In a Cochrane review of three studies and 103 cases it was concluded that β-mimetic therapy appears to be able to reduce the number of foetal heart rate abnormalities. The limited evidence suggests that β-mimetics are a useful treatment for 'buying time' in cases of foetal distress to prepare operative delivery or patient transfer. However, there is not yet enough evidence-based information on the effect of tocolysis as regards the need for operative delivery in cases of foetal distress (Kulier and Hofmeyr 2000).

Well-tolerated tachycardia is the only side-effect detected after short-lasting β-adrenergic tocolytic therapy in most studies (Mendez-Bauer et al. 1987, Patriarco et al. 1987, Cook and Spinnato 1994, Kulier et al. 1997, Thurlow and Kinsella 2002). In some studies, a moderate change in diastolic blood pressure has also been reported (Caritis et al. 1985, Hidaka et al. 1987, Burke et al. 1989, Shekarloo et al. 1989). In a prospective study (n=10) no negative short-term effects on foetal carbohydrate metabolism were seen when a single dose of terbutaline was given during labour (Ingemarsson et al. 1981).

7.5.4 Tocolytic therapy with nitroglycerin

The tocolytic effect of nitroglycerin is mediated via nitric oxide (NO) donation. Nitric oxide activates the synthesis of cyclic guanosine monophosphate (cGMP). This activates protein kinases, which leads to dephosphorylation of myosin light chains and ensuing smooth muscle relaxation (Smith and Brien 1998).

Nitroglycerin is mainly used as a uterine relaxant in cases of placental extraction, difficult foetal extraction during CS or vaginal delivery or external version of foetus (Axemo et al. 1998, Smith and Brien 1998, O'Grady et al. 2000). One prospective study on nitroglycerin use in intrapartum foetal distress related to uterine hyperactivity showed complete effectiveness in 22/24 cases and a partial effect in the remaining two cases. In 62% a single intravenous dose

(0.6–0.9 mg) was given; in 38% a second dose was required (Mercier et al. 1997).

The advantages of nitroglycerin are rapid onset, brief half-life and safety. Maternal hypotension can occur after nitroglycerin administration, but it is reversible with ephedrine (Mercier et al. 1997).

7.5.5 Tocolytic therapy with oxytocin antagonist

Atosiban binds to the oxytocin receptor and blocks its action on G-protein. By means of suppression of the enzyme phospholipase C, inhibition of calcium ion release is achieved, leading to muscle relaxation (Chandraharan and Arulkumaran 2005). The half-life of atosiban is short, 18 ± 3 minutes (Goodwin et al. 1995).

In a recent prospective randomised trial the oxytocin antagonist atosiban was found to be as effective as hexoprenaline for stopping contractions in cases of intrapartum foetal distress. Maternal tachycardia was less common in the atosiban group. Considering the low incidence of maternal adverse effects, atosiban may be a new option for acute intrapartum tocolysis (Afschar et al. 2004).

7.6 Paracervical block for labour analgesia in the first stage of labour

Labour pain is one of the most intensive pains one can experience (Lowe 2002). Epidural and spinal block and combined spinal-epidural analgesia for labour pain relief have been widely examined, recommended and accepted as superior pain relief methods (Ranta et al. 1994, Thorp and Murphy-Dellos 1998, ACOG 2002, Eltzschig et al. 2003). However, some parturients also desire alternative pharmacological and non-pharmacological pain relief methods (Thorp and Murphy-Dellos 1998, Caton et al. 2002, Lowe 2002). Paracervical block (PCB) is a pain relief method for parturients who wish for less invasive analgesia and who need rapid pain relief. It is also useful in situations where regional analgesia is contraindicated, for example because of a low platelet count, and in delivery units where regional analgesia is not available 24 hours a day.

PCB is simple, rapid, easily available and cost-effective, and does not interfere with the normal progression of labour (Ranta et al. 1995, Nieminen and Puolakka 1997, Thorp and Murphy-Dellos 1998). Some elements of concern, i.e. foetal adverse effects, especially post-PCB bradycardia and even foetal loss with the former deep injection technique, have limited the use of PCB in many countries (Nyirjesy et al. 1963, Teramo and Widholm 1967, Rosen 2002). With the new low-dose superficial injection technique handled by an experienced obstetrician PCB has been found to be safe and has a place in modern obstetrics (Jägerhorn 1975, Carlsson et al. 1987, Ranta et al. 1995).

7.6.1 Technique of paracervical block

Paracervical block is a regional analgesia technique that interrupts uterine sympathetic afferent activity through the posterior cervical and superior hypogastric plexuses (Paech 2003). It is given by an obstetrician transvaginally when the presenting part is well in the pelvis and the cervix is in the accelerated phase of dilatation. The obstetrician palpates the cervix and with a Kobak needle penetrates the endopelvic fascia to inject the anesthetic drug into the base of the broad ligament space (Kobak and Sadove 1962, Kobak et al. 1962). During injection the mother lies supine with her knees flexed and hips fully abducted.

The instrument used for the procedure was originally introduced in 1960 by Kobak and Sadove. This intrument, Kobak´s needle, has a round-tipped sheath that can be introduced to the injection site safely and without injury to the mother or foetus. After introducing the rounded tip to the injection site, the needle is pressed forward in the sheath, which controls and limits the depth of penetration. In the original instrument the limit was 15–20 mm. In modern obstetrics, for safety reasons the injection depth has been limited to 3–4 mm (Jägerhorn 1975). After careful aspiration the analgesic agent is injected at two different points: 3 and 9 o'clock or 4 and 8 o'clock. It has been shown in roentgenographic studies, that both these injection sites are equal in effectiveness because dispersion of the drug is identical in the base of the broad ligament space (Kobak et al. 1962). An alternative method is to administer the injection at four sites (3, 4, 8 and 9 o'clock). In some studies four-site administration has been shown to be more effective and reliable than two-site injection (Saloheimo 1968). The injection is given between contractions. After injection the mother turns over to a lateral position. The most widely used drug in PCB is 0.25% racemic bupivacaine, at a total dose of 10 ml (Ruther 1977, Meis et al. 1978, Read and Miller 1979, Achiron et al. 1987, Carlsson et al. 1987, Räsänen and Jouppila 1994, Ranta et al. 1995, Nieminen and Puolakka 1997).

7.6.2 Safety aspects of paracervical block

7.6.2.1 Post-PCB bradycardia

Bradycardia rates after PCB in some studies, with a superficial (2–4 mm) injection technique and mild concentrations (0.25% or less) of bupivacaine are shown in Table 2. A total of 1110 PCB´s are included, with the bradycardia rate in most studies being 2% or lower; in two smaller studies 5–12%. All cases of bradycardia in these studies were transient and no maternal complications were found.

Table 2 *The rate of bradycardia in former studies on PCB*

Study	*n*	Rate of bradycardia (%)	Duration of bradycardia
Jägerhorn (1975)*	204	1	Transient
Meis et al. (1978)*	53	0	
Grenman et al. (1986)*	39	5	1-8 min
Carlsson et al. (1987)**	469	2	6.5±1.7 min
Ranta et al. (1995)*	248	2	4-12 min
Nieminen and Puolakka (1997)**	97	12	Mild, transient

*PCB with 0.25% bupivacaine

**PCB with 0.25or 0.125% bupivacaine

Reprinted from Palomäki O, Huhtala H, Kirkinen P: A comparative study of the safety of 0.25% levobupivacaine and 0.25% racemic bupivacaine for paracervical block in the first stage of labour. Acta Obstet Gynecol Scand, in press, with permission from Blackwell Publishing.

Increased uterine activity, vasoconstriction of the uterine arteries and a direct effect on the foetal myocardium via the umbilical circulation have been proposed as explanations for bradycardia after PCB (Carlsson et al. 1987, Räsänen and Jouppila 1994). Paracervical block with Kobak´s needle and superficial injection given by an skilled obstetrician has lowered the previously high rates of bradycardia.

In studies on intrathecal labour analgesia, bradycardia rates of 5–7.7% have been reported, these being higher than bradycardia rates in most PCB studies (Palmer et al. 1999, Mardirosoff et al. 2002).

7.6.2.2 Foetal oxygen saturation and neonatal umbilical artery pH values after PCB

In a prospective study twenty healthy parturients were enrolled in PCB or epidural groups according to their preferences and clinical situation. These two analgesia methods were evaluated with respect to foetal oxygenation measured by means of a foetal oxymeter. In the PCB group, foetal oxygen saturation was slightly but not significantly elevated versus the baseline and versus the epidural group. There were no differences in maternal oxygen saturation (Kaita et al. 2000).

Only one prospective study on the effect of PCB on neonatal umbilical artery pH values can be found in the literature. In linear regression analysis, PCB use was not associated with low umbilical artery pH in 238 cases of labour analgesia, of which 126 were PCB´s (Levy et al. 1999).

7.6.2.3 Haemodynamic effects of PCB

Two studies where foetal and maternal blood flow were measured by Doppler ultrasonography before and after PCB have been published. In the first one, twelve parturients with uncomplicated pregnancies were included. Doppler ultrasonographic measurements of maternal uterine arteries and the foetal umbilical artery were obtained before, and one and twenty minutes after PCB with bupivacaine. Pulsatility indices (PIs) of uterine arteries did not change, and the PI values in the umbilical artery were not affected in cases with normal CTG patterns. In two cases, post-PCB bradycardia developed, and in these cases a marked increase in the PI of the umbilical artery and a minor increase in the PI values of the uterine arteries was seen; however, the blood velocity waveforms retuned to baseline after normalisation of the CTG pattern (Räsänen and Jouppila 1994).

In another study, 44 primiparous parturients were randomised to receive either PCB or epidural labour analgesia. Pulsatility indices of the maternal femoral and uterine arteries and foetal umbilical and middle cerebral arteries were measured before and after analgesia. The PI of the maternal femoral artery decreased after epidural analgesia and remained unchanged after PCB. The PI of the maternal uterine artery was unchanged after epidural analgesia but after PCB there was an increase. No differences in foetal circulation were found after either form of analgesia (Manninen et al. 2000).

7.6.2.4 Complications of regional analgesia

Parturients having PCB for labour analgesia are not exposed to complications that are typical of regional anaesthesia. According to ACOG, parturients with regional analgesia show the following rates: hypotension, 8.5–67%, fever among primiparous women, 19%, postdural puncture headache, 1–3% and pruritus, 1.3–85% (ACOG 2002). Labours with epidural analgesia are also associated with a lower rate of spontaneous vaginal delivery, a higher rate of instrumental vaginal delivery (Lieberman and O'Donoghue 2002) and a longer second stage of labour (Leighton and Halpern 2002) compared with labours without epidural analgesia. Paracervical block does not interfere with the normal progress of labour (Westholm et al. 1969, Read and Miller 1979, Thorp and Murphy-Dellos 1998).

7.6.2.5 Neonatal neurobehavioural effect of PCB

In a study reported by Kangas-Saarela *et al.* (1988), ten neonates whose mothers had PCB for pain relief during labour and twelve neonates whose mothers delivered without analgesia were compared as regards neurobehavioural responses at the ages of three hours, one day, two days and 4–5 days. No statistically significant differences were found between these groups in behaviour or neurological recovery after delivery.

7.6.3 Efficacy of paracervical block

Only a few studies can be found in which PCB has been compared with other pain relief methods. In a small study of 62 parturients, 39 chose PCB for pain relief and 23 chose epidural analgesia. Pain intensity was assessed on a scale of 0 to 10. Pain score values decreased significantly within 5 minutes in the PCB group and within 30 minutes in the epidural group. The analgesic effect was significantly better in the epidural group 30, 45 and 60 minutes after analgesia (Grenman et al. 1986). In another study, in which the pain relief method was randomised for 44 parturients, excellent or good pain relief was achieved in 87% of cases in the epidural group and in 67% of cases in the PCB group (Manninen et al. 2000). In a recent inquiry form study, out of 615 parturients in a PCB group and 1389 in an epidural group, the efficacy of pain relief was stated to be good in 57% in the PCB group and 75% in the epidural group, moderate in 27% in the PCB group and 17% in the epidural group and poor in 17% in the PCB group and 8% in the epidural group (Sarvela et al. 2005).

In a double-blind, randomised study, PCB with bupivacaine was compared with intramuscular meperidine. The average pain relief in the PCB group was significantly higher than in the meperidine group at 20, 40 and 60 minutes after administration of the drugs (Jensen et al. 1984).

In studies on PCB only, and using verbal rating, excellent or good pain relief has been reported in 59% (Ranta et al. 1995), 69% (Levy et al. 1999), 76% (Puolakka et al. 1984) and 94% of cases (Jägerhorn 1975) and poor pain relief in 12% (Puolakka et al. 1984), 13% (Ranta et al. 1995) and 18% of cases (Levy et al. 1999).

7.6.4 Levobupivacaine as an analgesic agent

In animal studies, levobupivacaine, the S(-)-enantiomer of racemic bupivacaine, has been found to be associated with lower risks of cardiovascular and CNS toxicity compared with racemic bupivacaine (Huang et al. 1998, Foster and Markham 2000). In many clinical studies the analgesic effect of levobupivacaine has been found to be equivalent to that of racemic bupivacaine (Vercauteren et al. 2001, Cheng et al. 2002, Camorcia and Capogna 2003, Faccenda et al. 2003, Kuczkowski 2004). In these studies levobupivacaine was compared with racemic bupivacaine in epidural anesthesia for CS and epidural and intrathecal labour analgesia. Levobupivacaine is in practical use in epidural and intrathecal analgesia (Robinson et al. 2001, Capogna and Camorcia 2004, Lim et al. 2004) but not yet widely in PCB.

7.7 Cardiotocography for intrapartum foetal monitoring

7.7.1 Foetal oxygenation, stress and distress

The foetus receives oxygen via the placenta and is thus dependent on continuous and adequate uterine blood flow. There are several physiological compensation mechanisms to protect the foetus from acidosis and alkalosis. Firstly, foetal erythrocytes mostly contain haemoglobin F, which binds more oxygen than adult haemoglobin (haemoglobin A). This functional difference occurs at any given oxygen tension at an identical pH. On the other hand, the stimulatory effect of progestin on the maternal respiratory centre results in respiratory alkalosis. Plasma bicarbonate levels decrease, resulting in a minimal increase of blood pH. This increase shifts the oxygen dissociation curve to the left and increases the affinity of maternal haemoglobin for oxygen. This compensation mechanism is called the Bohr effect. Reduced maternal P_{CO2} facilitates transport of carbon dioxide from the foetus to the mother and impairs the release of oxygen from mother to foetus. However, the increase in blood pH stimulates an increase in 2,3-diphosphoglycerate in maternal erythrocytes, counteracting the Bohr effect by shifting the oxygen dissociation curve back to the right and facilitating oxygen release to the foetus (William's Obstetrics 2005).

Other foetal compensation mechanisms against hypoxia (lack of oxygen at the tissue level) and asphyxia (hypoxia with metabolic acidosis) include decreased activity and growth, and redistribution of blood flow to the most important areas (heart, brain and adrenal glands) (Sundström et al. 2000). In spite of compensatory mechanisms, labour or intrapartum complications can alter foetal oxygenation, leading to foetal stress or even to foetal distress. Foetal stress is a potentially pre-pathological situation, which the foetus in normal conditions can tolerate, and which is manifested by CTG changes. Foetal stress can lead to distress, which is a pathological phenomenon in which hypoxia leads to asphyxia. Duration of asphyxia correlates with severity of neonatal complications. The development of distress depends on pre-existing foetal and maternal status, gestational age, intensity and duration of the stress, and ability of caregivers to assess the foetal condition and react appropriately (ACOG 1995, Cibils 1996, Huddleston 1999). The goal of obstetric staff should be appropriate identification and management of foetal stress and intervention before the development of foetal distress (Dellinger and Boehm 1995, Cibils 1996).

Continuous CTG monitoring during labour has been common practice in developed countries in recent decades. Several studies have shown associations between CTG pathology and foetal acidosis (Low et al. 1999, Hadar et al. 2001, Williams and Galerneau 2003, Sameshima et al. 2004), elevated cord nucleated red blood cell count, which is a predictor of adverse foetal outcome (Ferber et al. 2003, Ferber et al. 2005), and perinatal seizures (Thacker et al. 1998, Thacker et al. 2001, Williams and Galerneau 2004).

7.7.2 Technique of cardiotocography

Monitoring of intrapartum cardiography is usually performed with intrauterine electrode. In internal monitoring, a skin-penetrating spiral electrode is placed directly on the foetal presenting part. This records the beat-to-beat interval by peak detection of the QRS of foetal electrocardiography (ECG) and counts FHR. External recording involves use of a Doppler device and is used in cases of intact membranes or when a non-invasive technique is preferred, for example because of maternal viral infection. External monitoring requires belts on the maternal abdomen for the transducers, and can give a poorer picture of FHR variability. Signal loss can be masked, or, on the other hand, recording gaps can occur during maternal or foetal movements (ACOG 1995, FIGO 1995, FIGO 1997, Huddleston 1999).

The method of tocography is described above (*Measurement and evaluation of contractions*). In both external and internal monitoring, the FHR is recorded continuously on the upper part and tocometry on the lower part of the paper, and the commonly used speed of the paper is 1 cm/minute.

7.7.3 Interpretation of cardiotocography

Certain CTG patterns are associated with specific changes in foetal condition. In clinical situations, different forms of terminology and misinterpretation of CTG's can lead to foetal compromise, or, on the other hand, to unnecessary intervention. In order to standardize the terminology in the interpretation of CTG's, the International Federation of Gynaecology & Obstetrics (FIGO) published (in 1987) guidelines for the use of foetal monitoring. Table 3 shows the classification criteria for intrapartum CTG according to FIGO. Ten years later the National Institute of Child Health and Human Development in the United States convened a panel of clinical experts to develop standardized research guidelines for CTG interpretation, which were published in 1997 (NICHHD 1997, Sandmire and DeMott 1998, Cibils 1998). Many other groups, such as the American College of Obstetricians and Gynecologists, have also created and published their own definitions and recommendations (ACOG 1995).

Table 3 *Definition of intrapartum CTG patterns according to FIGO*

Normal pattern	Baseline 110–150 bpm Amplitude of variability 5–25 bpm
Suspicious pattern (any of the following)	Baseline heart rate 150–170 bpm or 100–110 bpm Amplitude of variability 5–10 bpm for more than 40 min Increased variability > 25 bpm Variable decelerations
Pathological pattern (any of the following)	Baseline heart rate < 100 bpm or > 170 bpm Persistence of heart rate variability of less than 5 bpm for more than 40 min Severe variable decelerations or severe repetitive early decelerations Prolonged decelerations Late decelerations; the most ominous trace is a steady baseline without baseline variability and with small decelerations after each contraction A sinusoidal pattern for 20 min or longer with the following characteristics: regular with cyclic changes in the baseline such as a sine wave; frequency less than 6 cycles/min; amplitude at least 10 bpm
Pathological uterine activity	More than 5 contractions per 10 min

FIGO = International Federation of Gynaecology and Obstetrics

bpm = beats per minute

7.7.4 Inter-observer variation in CTG interpretation

Several studies on inter-observer agreement in the assessment of intrapartum (Beaulieu et al. 1982, Nielsen et al. 1987, Keith et al. 1995), antepartum (Trimbos and Keirse 1978, Lotgering et al. 1982), both ante- and intrapartum (Lidegaard et al. 1992, Donker et al. 1993, Bernardes et al. 1997, Ayres-de-Campos et al. 1999, Ayres-de-Campos and Bernardes 1999, Ayres-de-Campos et al. 2004) and labour admission test CTG´s (Blix et al. 2003) have been published. In the studies on intrapartum CTG interpretation, various classification systems for CTG, estimated foetal conditions and clinical decisions based on CTG have been used. The amounts of clinical information, the experience of the clinicians involved and the proportions of pathological tracings among the study material, as well as statistical methods for interpreting the results differ from each other. Table 4 shows the conclusions in some studies on inter-observer variation in the interpretation of intrapartum CTG's.

Table 4 *Studies on interobserver variation in the interpretation of intrapartum CTG*

Ref	CTG´s (n)	Observers (n)	Classification of CTG and/or fetal condition	Categories of classification (n)	Classification of clinical decision	Result
1	150	5	Normal-suspect-abnormal CTG	3		All observers agreed in 29%
2	50	4	Normal-pathological CTG	2		Pairvice interobserver agreement 69%
3	11	116	1. Description of 9 elements of CTG	2	CS or not	Agreement 49.7-94% for different FHR changes
			2. Non-slightly-moderately-severely stressed fetus	4		Agreement 63.9% (senior)- 59.3% (junior) for fetal condition Agreement 69.5% for CS decision
4	50	17			5-step scoring for concern of fetus and management	Agreement 70%
5	17	3	7 classification codes for CTG	2		Pa for baseline variability 0.63 Pa for accelerations 0.56 Pa for decelerations 0.51 Pa for variability 0.13-0.64 Pa for type of deceleration 0.24-0.31
6	17	3	Normal-suspicious-pathological CTG according to FIGO guidelines	3	No action-monitoring-intervention	For CTG classification Pa 0.62 for normal and 0.25-0.42 for abnormal tracings For clinical decision Pa 0.79 for no action 0.14 for close monitoring and 0.38 for intervention
7	33	3	Early-variable-late deceleration in CTG	2		Pa for early deceleration 0.36 Pa for variable deceleration 0.27 Pa for late deceleration 0.31
8	22	31	Description of 8 elements of CTG	2	Intervention or not	Results shown in Table 11.

1 Beaulieu et al. (1982)
2 Nielsen et al. (1987)
3 Lidegaard et al. (1992)
4 Keith et al. (1995)
5 Bernades et al. (1997)
6 Ayres-de-Campos et al. (1999)
7 Ayres-de-Campos and Bernardes (1999)
8 Study V

As can be interpreted from the results in Table 4, inter-observer agreement varies from poor to good depending on the study, classification and statistical method used. Agreement has been found to be better for normal tracings and poor for suspicious and pathological tracings (Ayres-de-Campos et al. 1999). Especially poor agreement has been found in assessment of baseline variability and type of deceleration (Lidegaard et al. 1992, Donker et al. 1993, Bernardes et al. 1997, Ayres-de-Campos and Bernardes 1999). The deficiency in inter-observer reproducibility has been construed to depend on lack of use of equivocal terminology and definitions, although guidelines exist (FIGO) (Donker et al. 1993, Bernardes et al. 1997), and also on human visual and methodological inaccuracy (Bernardes et al. 1997).

Misinterpretation of CTG data or inappropriate action in the presence of CTG pathology are the most common person-based problems in labour ward (Lakasing and Spencer 2002, Williams and Arulkumaran 2004). Various training and audit systems have been developed to minimize these kinds of risk, including developing and maintaining a local CTG training programme and regular feedback meetings (Young et al. 2001), telemedicine CTG interpretation sessions for trainee registrars in obstetrics and gynaecology, and their consultants and midwives (Morris 2000), and computer-assisted teaching programmes for intrapartum foetal monitoring (Beckley et al. 2000). In a recent review on medico-legal issues concerning CTG, regular and compulsory training, guidelines and appropriate management options, electronic archiving systems, rapid review of adverse events and regular audit of adverse outcomes as well as ready access to foetal scalp blood sampling and umbilical cord artery pH measurement were recommended for all maternity units (Williams and Arulkumaran 2004).

7.7.5 Additional methods of intrapartum foetal surveillance

An abnormal CTG reading does not always mean foetal hypoxia. In order to improve CTG specificity and to avoid unnecessary Caesarean sections, foetal scalp blood samples have been recommended as a routine procedure in cases with suspicious CTG patterns (Jibodu and Arulkumaran 2000). Other additional tools include foetal pulse oximetry (Kuhnert et al. 1998, Puertas et al. 2004), measurement of scalp lactate levels (Westgren et al. 1999), computer analyses by means of automated foetal heart rate monitoring systems (computerized CTG, cCTG) (Keith et al. 1995, FIGO 1997, Devoe et al. 2000, Liszka-Hackzell 2001) and, with very promising results, computer-based ST waveform analysis of foetal electrocardiography combined with CTG. This method has been shown to provide accurate information on intrapartum hypoxia similar to that obtained by scalp pH, and to reduce the incidence of umbilical artery metabolic acidosis and marked neurological symptoms in newborns (Amer-Wåhlin et al. 2001, Noren et al. 2003, Luttkus et al. 2004, Rosen et al. 2004). In two recent studies a better inter-observer agreement rate for decision-making and timing of intervention

was found with CTG and ST-analysis than with CTG alone (Ross et al. 2004, Amer-Wåhlin et al. 2005).

8 AIMS OF THE STUDY

The purpose of this study was to evaluate the applicability and safety of some pharmacological agents used to activate or inhibit labour contractions and used in labour analgesia. Special aims were:

1. To evaluate the applicability and safety of the intravenous β-blocking drug propranolol combined with oxytocin in comparison with oxytocin alone in arrested first stage of labour (Study I)

2. To evaluate the effects of acute intravenous tocolysis with the β-mimetic agents ritodrine hydrochloride or bufenine hydrochloride on severely abnormal CTG patterns during the first stage of labour, and to investigate whether or not it is possible to discover clinical factors associated with normalisation of abnormal CTG patterns (Study II)

3. To evaluate the applicability of levobupivacaine as a PCB agent in comparison with racemic bupivacaine. In particular, the safety aspects of these two agents, reflected by cardiotocographic abnormalities and perinatal outcome, were analysed (Study III)

4. To evaluate the analgesic effect of paracervical block in labour pain relief and to discover the determinants associated with good analgesia (Study IV)

5. To evaluate inter-observer agreement in the visual interpretation of intrapartum CTG readings and recommendations for intervention (Study V)

9 SUBJECTS AND METHODS

9.1 Subjects

All women who participated in the study did so voluntarily after giving written informed consent. In prospective studies I, III and IV the Ethics Committee of Tampere University Hospital and the Finnish Drug Council approved the study protocol. In retrospective study II and questionnaire study V permission from Tampere University Hospital Ethics Committee was granted.

The subjects were all women delivering between years 2001 and 2004 at the Department of Obstetrics and Gynaecology, Tampere University Hospital, which is a tertiary university clinic in Tampere, Finland. In 2004 the number of deliveries was 4783. The overall CS frequency was 15.1%, and vacuum frequency 7.3%. Paracervical block was given to 29.3% and epidural or spinal analgesia to 52.5% of the parturients. Oxytocin was used in 54.0% of the deliveries.

The study material, design, objectives and outcome measures in studies I–V are shown in Table 5.

Table 5 *Study material, design, objectives and outcome measures in Studies I–V*

Study no.	Number and characteristics of subjects	Objective	Length of gravidity
Study I	107 Failure to progress in the first stage of labour	To compare the combination of intravenous propranolol and oxytocin with oxytocin only in augmentation of labour	≥ 37 weeks
Study II	73 Severe CTG abnormalities in the first stage of labour	To evaluate the effect of acute tocolysis on severe pathological CTG readings during the first stage of labour	≥ 37 weeks
Study III	40 + 397 Normal course of pregnancy and normal latent phase of labour	To evaluate and compare the safety of levobupivacaine and racemic bupivacaine in PCB's given during the first stage of labour	37–42 weeks
Study IV	341 Normal course of pregnancy and normal latent phase of labour	To evaluate the analgesic effect of PCB in labour pain relief and to discover the determinants associated with good analgesia	37–42 weeks
Study V	31 obstetricians assessing 22 intrapartum CTG´s	To examine the level of inter-observer agreement in visual interpretation of intrapartum CTG readings and recommendations for intervention	35–42 weeks

Table 5 *Study material, design, objectives and outcome measures in Studies I-V*

Study no.	Main outcome measure	Secondary outcome measures	Design
Study I	Effect of intravenous propranolol on the frequency of CS among parturients with arrested labour	Duration of labour, required dosage of oxytocin, CTG readings, neonatal outcome and maternal and cord plasma levels of propranolol	Prospective Randomised Double-blind
Study II	Normalisation or persistence of abnormal CTG patterns after tocolysis	Clinical factors associated with normalisation of abnormal CTG patterns	Retrospective
Study III	Safety of levobupivacaine versus bupivacaine reflected by CTG abnormalities and perinatal outcome	Analgesic effect between levobupivacaine and bupivacaine Delivery outcome after PCB	Open pilot Double-blind Randomised
Study IV	Determinants associated with good analgesia	Incidence of post-PCB bradycardia in CTG, and neonatal outcome	Prospective
Study V	Inter-observer agreement assessed by proportions of agreement (Pa) concerning interpretation of 8 elements of CTG and and recommendation for intervention	Differences in Pa between junior and senior obstetricians and obstetricians from different delivery clinics	Questionnaire

9.2 Methods

9.2.1 CTG recording and interpretation

In studies I–V the CTG readings were recorded by means of Hewlett Packard 50IP or 50XM equipment (Hewlett-Packard, Geneva, Switzerland) with an intrauterine scalp electrode. In some cases an intrauterine liquid-filled pressure measurement catheter Philips 14099E (Philips Medizin-systeme, Boeblingen, Germany) was used.

In studies I–IV, a specialist obstetrician, who was blind to the study drugs and neonatal outcome, carried out detailed analysis of the CTG patterns.

In studies I, III and IV the occurrence of abnormalities in the CTG readings was analysed. The observed abnormalities were absence of accelerations, decreased variability (variability of less than five beats per minute (bpm) for more than five minutes), late decelerations and bradycardia (a decrease of mean foetal heart rate of at least 20 bpm or an absolute rate of less than 100 bpm for two minutes or more).

In study II, the criteria for severity of CTG pathology included constant bradycardia (more than 20 beats/min below baseline) for 2 minutes or more, repeated (five or more in 30 minutes) variable decelerations, late decelerations and complicated variable decelerations with one or more warning signs: missing or emphasized acceleration before and after deceleration, prolonged return to baseline, decreasing baseline or compensatory tachycardia after deceleration, U-shaped deceleration, decreased variability at the bottom of deceleration, and biphasic deceleration (Ingemarsson and Ingemarsson 1987, Huddleston 1999).

In study V, the obstetricians were asked to answer questions about baseline, reactivity, uterine tonus, power of contractions (normal/abnormal), early, variable and late decelerations and hypertonus (yes/no).

In studies I-IV the power of contractions was measured in Montevideo units in cases where intrauterine pressure measurement was used. According to Caldeyro-Barcia *et al.* (1957) the intensity (amplitude) of contraction is measured by the rise in pressure (mmHg) from baseline. The intensity is coupled to contraction frequency per 10 minutes. The product (intensity × frequency) is called uterine activity and is expressed in Montevideo units.

A summary of the focus of interests concerning CTG pathology in the studies is shown in Table 6.

Table 6 *Observed CTG abnormalities in studies I–V*

Study	Cardiography	Tocography
I	Absence of accelerations	Rate of contractions
	Decreased variability	Power of contractions
	Late decelerations	
	Bradycardia	
II	Late decelerations	Power of contractions
	Bradycardia	Uterine hypertonus
	Repeated variable decelerations	
	Complicated variable decelerations	
III	Absence of accelerations	Rate of contractions
	Decreased variability	Power of contractions
	Late decelerations	
	Bradycardia	
IV	Bradycardia	
V	CTG baseline	Uterine tonus
	Variability	Power of contractions
	Early, variable and late decelerations	Hypertonus

9.2.2 Study drugs

In study I, double-blind randomisation was based on a computer-generated list. Propranolol (2 mg (2ml) in 98 ml saline) (study drug) or 100 ml saline (placebo) was infused intravenously over a 10-minute period. Oxytocin infusion was started at the same time, at 2.5 mIU/minute, and this was raised by 2.5 mIU/minute every 30 minutes until the contractions reached 150 Montevideo units.

In study II, the drug used in 73% of the cases was 50 mg ritodrine hydrochloride in 500 ml 5% glucose and in 27% of the cases it was 50 mg bufenine hydrochloride in 500 ml 5% glucose. The infusion rate for both drugs was 300 ml/h. If previously used, oxytocin infusion was stopped before tocolytic therapy.

In studies III and IV, paracervical block was given transvaginally by means of 10 ml of 0.25% levobupivacaine or 0.25% racemic bupivacaine.

9.2.3 Measurement of maternal and cord plasma levels of propranolol

In study I, levels of propranolol in maternal and foetal (umbilical artery) plasma were measured among the first 30 cases in the propranolol group immediately after delivery. The concentrations of the beta-adrenoceptor-binding component of propranolol were determined by using a radio-receptor assay. The assay

primarily measures the levo-enantiomer of parent propranolol and the levo-enantiomer of 4-OH-propranolol, which bind with high affinity to beta-adrenoceptors. The sensitivity of the assay for racemic propranolol is 0.4 ng/ml with intra- and inter-assay variation of less than 10% (Kaila and Marttila 1993).

9.2.4 Paracervical block

In studies III and IV, paracervical block was given transvaginally using a modification of Kobak´s needle. With this needle it is possible to penetrate the endopelvic fascia into the base of the broad ligament space and then limit the depth of drug injection to 3–4 millimetres. 2.5 ml of 0.25% levobupivacaine or 0.25% racemic bupivacaine was injected into the lateral fornix of the vagina at four different points: 3, 4, 8 and 9 o'clock (total 10 ml). During injection the mother lay on her back with her knees flexed and hips fully abducted. After injection she turned over to a lateral position. The injections were given between contractions within 1–3 minutes.

9.2.5 Visual Analogue Scale

In study IV, pain intensity was assessed by means of a Visual Analogue Scale (VAS), which is a 100 mm-long horizontal line, the left end (0 mm) meaning no pain and the right end (100 mm) meaning the highest imaginable pain. The parturient was asked to draw a vertical mark on the line before, and 5, 15, 30, 45, 60 and 90 minutes after PCB.

Pain intensity measurement by VAS has been criticized because of inter-individual differences in interpretation of maximal pain (Lowe 2002). To reduce the effect of variation in pain scoring, the factors associated with good pain relief were evaluated in two groups: the group where there was more than a 50% decrease in the VAS score within 30 minutes (good response) and the group where there was less than a 50% decrease in the VAS score within 30 minutes (non-optimal response).

9.2.6 Statistical methods

In studies I–IV, categorial variables between the groups were compared using Chi square and Fisher's exact tests. Continuous variables were compared using the Mann-Whitney *U*-test and Student's *t*-test.

In study III, the 95% confidence intervals for between-group differences were calculated by Newcombe's method.

In study IV, the factors associated with good pain relief were calculated by logistic regression analysis. For pair-wise comparisons Wilcoxon's signed rank test was used.

In studies I–IV, all statistical analyses were performed using SPSS for Windows, version 11.0 (SPSS Inc., Chicago, Illinois, USA).

In study V, inter-observer agreement was assessed by the proportions of agreement (Pa) method, with 95% confidence intervals (CIs), as described by Grant (1991). The method is based on the limits of agreement method described by Bland and Altman (1986). According to Grant, if the 95% CI of the proportion of agreement includes 0.5 or is less and sample size is adequate, the agreement should be considered poor.

The number of trials of agreement for *n* observers is 1+2+…+ (*n*-1). In study V, with 31 observers, there were 465 trials of agreement for each CTG reading. With all 22 readings and all 31 observers there were 10 230 trials of agreement. The table of agreement was in the form:

	Observer B	
Observer A	Normal	Abnormal
Normal	e	f
Abnormal	g	h

The proportion of agreement for normality is $p = e/(e + f + g)$. To estimate the proportion of agreement for normality between the observers for the whole group of CTG's the 95% confidence interval of the proportion of agreement for the sample was calculated from the standard error of the proportion by

$SE = \sqrt{(p(1-p)/n}$, where $n = e + f + g$.

The 95% CI is $p \pm 1.96xSE$ according to a standard normal distribution. Bias for multiple observers was assessed by Cochran's test, which tests the null hypothesis that bias among the observers is not significantly different from zero. Cochran's test and calculation of frequencies of assessments and agreements were carried out using SPSS for Windows software, version 12.0.1 (SPSS Inc., Chicago, IL, USA).

10 RESULTS

10.1 Effect of propranolol on the frequency of Caesarean section, length of labour and power of contractions

In spite of arrested dilatation before medication, the overall Caesarean section rate was low in the whole population, and no reduction in CS rate or vacuum extraction rate was found in the propranolol group compared with the placebo group. The delivery characteristics in the groups are shown in Table 7.

Table 7 *Delivery characteristics in Study I*

	Propranolol *n*=55	Placebo *n*=52	*p* value*
Spontaneous vaginal	40 (73%)	44 (85%)	
Vacuum extraction	9 (16%)	6 (11%)	0.331
Caesarean section	6 (11%)	2 (4%)	0.154
Indication for vacuum			
Prolonged second stage	0	2	
Asphyxia imminens	3	2	
Malpresentation	0	1	
Exhaustio matris	6	1	
Indication for Caesarean			
Failure to progress	4	1	
Malpresentation	2	1	

*Fisher´s exact test.

Reprinted from Palomäki O, Uotila J, Tammela O, Kaila T, Lavapuro M, Huhtala H, Tuimala R: A double-blind, randomized trial on augmentation of labour with a combination of intravenous propranolol and oxytocin versus oxytocin only. Eur J Obst Gyn Reprod Biol, in press, with permission from Elsevier.

Cervical status was equal in both groups before augmentation. The absolute duration of the augmented part of labour was 38 minutes shorter in the propranolol group (median 185 vs. 223 minutes). This difference did not reach statistical significance (p=0.217; Mann-Whitney test). The total duration of

labour (1st, 2nd and 3rd stage) was 42 minutes longer in the propranolol group (median 810 vs. 768 minutes, p=0.486; Mann-Whitney test).

Among the women who delivered vaginally, the percentage proportions of the augmented part of labour out of the whole delivery were 21% and 29% in the propranolol group and the placebo group, respectively (p=0.023; Mann-Whitney test).

The power of contractions was weak in both groups before augmentation; the median power was 80 Montevideo units in the propranolol group and 93 Montevideo units in the placebo group. One hour after the start of augmentation the propranolol group reached a median of 158 Montevideo units and the placebo group 170 Montevideo units. At the beginning of the second stage of labour the median power of contractions was 230 Montevideo units in both groups. The differences between groups were not statistically significant at any point of time (p=0.13, 0.25 and 0.58 respectively; Mann-Whitney test).

10.2 Effects of propranolol on CTG readings, dosage of oxytocin and neonatal outcome

All CTG readings were analysed for a 60-minute period after the beginning of augmentation to investigate the incidence of CTG pathology. Pathological findings were rare. In the propranolol group there were two cases of transient bradycardia and no other pathological findings. In the placebo group there were also two cases of bradycardia, and in addition two cases of decreased variability and two cases of missing accelerations.

In all cases uterine hypercontractility was detected at the time of bradycardia. All cases of bradycardia were transient, lasting 3–5 minutes. The timing of the beginning of bradycardia was 10–12 minutes after propranolol administration and 13–36 minutes after placebo.

Among the 18 parturients who were given two doses of propranolol/placebo, the CTG baseline frequency was lowered by 10–15 bpm in two cases in the propranolol group and in three cases in the placebo group. Among the rest of the women baseline changes of less than five bpm were detected equally in both groups.

The median value of the maximum oxytocin infusion rate was 7.5 mIU/min in the propranolol group and it was 10 mIU/min in the placebo group, this difference not reaching statistical significance (p=0.234; Mann-Whitney test).

No significant differences between the propranolol and placebo groups in 1- or 5-minute Apgar scores, cord artery pH, base excess or lactate, blood pressure, pulse frequency, blood glucose level, breathing frequency or admission to a neonatal intensive care unit were found among the neonates. Six neonates in the propranolol group and five in the placebo group were treated in a neonatal intensive care unit after delivery. Analysis of these cases was carried out by a specialist paediatrician who was blind to the medication used. In this analysis,

six neonates had problems not connected to propranolol use, such as neonatal infection. Five neonates were admitted to a neonatal intensive care unit with diagnoses such as hypoglycaemia, transient tachypnoea, asphyxia or meconium aspiration syndrome, interpreted as potentially caused by propranolol. Among these five neonates, two had been exposed to propranolol and the other three had been in the placebo group.

10.3 Maternal and cord arterial plasma levels of propranolol

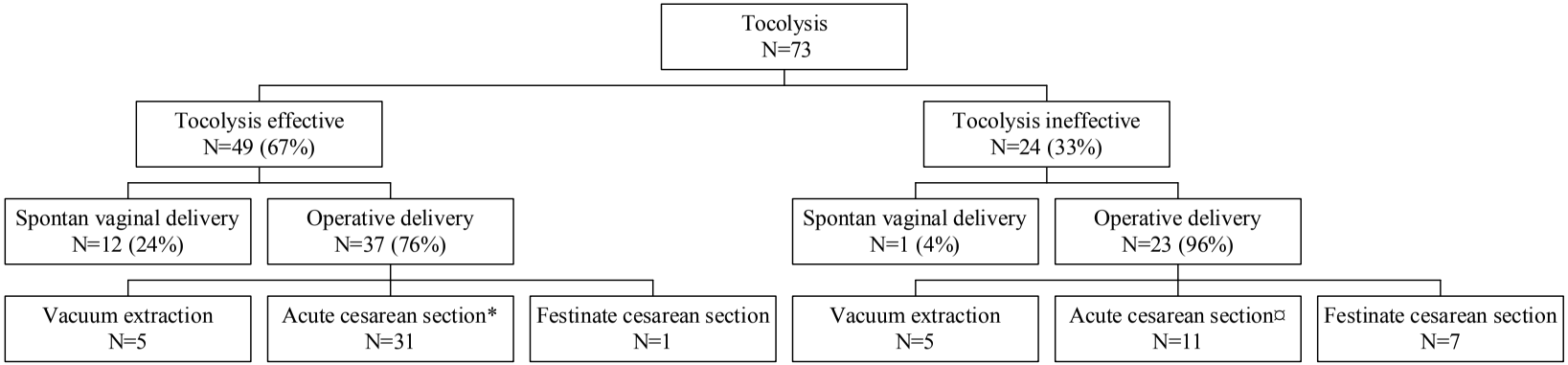
The concentrations of the beta-adrenoceptor-binding component of propranolol (levo-enantiomer of propranolol and levo-enantiomer of 4-OH-propranolol) after a 2 mg intravenous dose at the time of delivery were roughly similar in parturients and neonates. The maternal concentration, mean (range), was 3.8 mg/l (0.4–14.0 mg/l) and the neonatal concentration was 3.4 mg/l (0.5–13.2 mg/l), respectively. The active drug component readily crossed the placental barrier, with an average neonatal umbilical artery/maternal venous plasma ratio of 0.7 (0.2–3.7). In parturients who received two doses of 2 mg propranolol (n=5), there was no sign of drug accumulation after the repeated doses. The mean concentration in parturients after a 4 mg dose was 2.8 ng/ml (0.5–5.9 ng/ml). In neonates (n=4) there was a tendency towards higher active drug concentrations after the repeated dose than after the single 2 mg dose. The concentration after two doses of 2 mg propranolol, mean (range), was 4.1 ng/ml (1.8–5.9 ng/ml). Thus, propranolol may accumulate in neonates after repeated dosing. The beta-receptor-binding component exceeded 1.0 ng/ml in 14/23 parturients and 16/24 neonates. Concentrations exceeding 1 ng/ml are likely to exert minor beta-blocking effects in humans.

The study data was insufficient to construct a picture of the kinetics of the beta-adrenoceptor-binding component of propranolol.

10.4 Effect of tocolysis on severely pathological CTG patterns

Among the retrospective study material of 73 consecutive full-term (≥ 37 weeks) deliveries complicated by severe CTG abnormalities during the first stage of labour, the CTG pattern became normalised in 49 cases (67%), at 4 minutes (1-13 minutes), mean (range), after initiation of tocolytic therapy. This group was called the Tocolytic Effective (TE) group. Intravenous tocolysis was continued on average with decreasing doses for 35 minutes. In this group 12 mothers had spontaneous vaginal delivery, within 3 hours on average; there were five vacuum extractions and 32 Caesarean sections.

In 24 cases (33%) the CTG pattern did not become normalised. This group was called the Tocolysis Ineffective (TI) group. In 9 cases in this group the pattern improved partially but not totally, and in 15 cases there was no improvement. All but one woman underwent operative delivery, either CS or vacuum extraction, on average at 33 minutes after the beginning of tocolysis. The effectiveness of tocolysis and manner of delivery in the TE and TI groups is shown in Figure 5.



* = In 16 cases the decision to operate was made before the effect of tocolysis was observed
¤ = In 7 cases the decision to operate was made before tocolysis

Figure 5 *The effectiveness of tocolysis and mode of delivery in the Tocolysis Effective and Tocolysis Ineffective groups in Study II.*
Reprinted from Palomäki O, Jansson M, Huhtala H, Kirkinen P (2004): Severe cardiotocographic pathology at labor: effect of acute intravenous tocolysis. Am J Perinatol 21(6):347-53, with permission from Thieme.

The effectiveness or ineffectiveness of tocolysis was not found to be connected to any of the characteristics of the parturient, characteristics of labour or CTG. Oxytocin augmentation was given only in 11 cases within 60 minutes before tocolysis, and of these, tocolysis was effective in 10 cases and ineffective in one (p=0.090; Fisher's exact test).

The activity of uterine contractions before tocolysis was equal in both groups (median 200 Montevideo units in the TE group and 190 Montevideo units in the TI group). The effect of tocolysis on the Montevideo unit count was significantly better in the TE group than in the TI group: the decrease was 140 units vs. 95 units (p=0.035; t-test), respectively.

Uterine hypertonus (increase of uterine baseline tonus ≥ 20 mmHg or five or more contractions per 10 minutes) were present in 56% of cases in the TE group and 44% of cases in the TI group (p=0.165; Fisher's exact test) before tocolysis. Hypertonus disappeared during tocolysis in the TE group in 92% of cases and in the TI group only in 8% of cases (p=0.003; Fisher's exact test).

The pH was below 7.25 before tocolysis in 19 cases (15/31 (48%) in the TE group and 4/10 (40%) in the TI group), and normalised after tocolytic therapy in 15 cases (79%).

The incidence of various CTG pathologies in the TE and TI groups is shown in Table 8. There were no statistically significant differences between the groups in gestational age, birth-weight, 1- and 5-minute Apgar scores or umbilical artery pH values. The base excess in the umbilical artery was significantly better in the neonates in the TE group (mean -4.8 mmol/l vs. -6.8 mmol/l in the TE and TI groups, respectively; p = 0.045; Mann-Whitney test).

Blood loss at vaginal delivery on average was 500 ml (25^{th} percentile 300 ml and 75^{th} percentile 850 ml), and in the cases of Caesarean section, 625 ml (25^{th} percentile 400 ml and 75^{th} percentile 975 ml). Seventeen parturients received a single additional oxytocin injection to intensify contraction of the uterus during Caesarean section. A few parturients suffered from mild tachycardia; other side-effects of tocolytic therapy were not found.

Table 8 *The incidence of various CTG pathologies in the TE and TI groups in Study II*

CTG abnormality*	TE		TI	
	Yes	No	Yes	No
Constant bradycardia (more than 20 beats/min below baseline for 2 min or more)	75%	60%	25%	40%
Late decelerations	6%	5%	94%	95%
Repeated variable decelerations (5 or more per 30 minutes)	83%	90%	17%	10%
Complicated variable decelerations with one or more warning signs**	39%	25%	61%	75%

* Many patients had several CTG abnormalities

**The warning signs are listed in the Subjects and Methods section

TE = Tocolysis effective

TI = Tocolysis ineffective

Reprinted from Palomäki O, Jansson M, Huhtala H, Kirkinen P (2004): Severe cardiotocographic pathology at labor: effect of acute intravenous tocolysis. Am J Perinatol 21(6):347-53, with permission from Thieme.

10.5 Safety of levobupivacaine versus racemic bupivacaine in paracervical block

10.5.1 CTG abnormality after PCB

Before the randomised double-blind study a smaller open pilot study was carried out to characterise the usefulness and safety of levobupivacaine in PCB. Every second subject out of 40 had PCB with levobupivacaine, the remainder receiving racemic bupivacaine, and all PCB´s were given by a single obstetrician. Among these parturients, there were two cases of transient bradycardia in the racemic bupivacaine group, beginning 6 and 20 minutes after PCB and lasting for two and three minutes. Other pathological CTG results were not detected.

After the pilot study, applicability and safety aspects of levobupivacaine compared with racemic bupivacaine in routine obstetric practice were examined in a double-blind, randomised study involving 397 women and 440 PCB's. The PCB´s were given twenty-four hours per day by 27 resident and senior obstetricians. In this study the incidence of any CTG pathology in the 30-minute period after PCB was 10.4% in the levobupivacaine group and 12.8% in the racemic bupivacaine group (p=0.46; Fisher's exact test). All the CTG changes, including instances of bradycardia, were transient and no intervention was needed. Cardiotocographic pathology after PCB is shown in Table 9. Neonatal outcome in all the cases of post-PCB bradycardia was good, the mean umbilical artery pH being 7.35 in the levobupivacaine group and 7.28 in the racemic bupivacaine group. The mean base excess was -3 mmol/l in both groups. No admissions to neonatal care units were needed among the cases of post-PCB bradycardia.

Table 9 *Cardiotocographic pathology within the 30-minute period after PCB in study III*

	All PCB's	Levobupivacaine*	Racemic bupivacaine*	
	n=440	*n*=229	*n*=211	*p*-value
Absence of accelerations	3.2%	2.6%	3.8%	0.59
Decreased variability	4.1%	3.5%	4.7%	0.63
Late decelerations	1.1%	1.7%	0.5%	0.37
Bradycardia	3.2%	2.6%	3.8%	0.59
Any CTG abnormality	11.6%	10.4%	12.8%	0.46

* In both groups 3 PCB´s were followed by more than 1 CTG abnormality

Reprinted from Palomäki O, Huhtala H, Kirkinen P: A comparative study of the safety of 0.25% levobupivacaine and 0.25% racemic bupivacaine for paracervical block in the first stage of labour. Acta Obstet Gynecol Scand, in press, with permission from Blackwell Publishing.

10.5.2 Power of contractions after PCB

The median frequency of contractions before PCB was three per 10 minutes, and after PCB, four per 10 minutes in both groups.

Intrauterine pressure was registered in 52 cases (24 in the levobupivacaine group and 28 in the racemic bupivacaine group). The contractions were more powerful after PCB in both groups. The medians were 120 and 115 Montevideo units before PCB and 143 and 150 Montevideo units after PCB in the levobupivacaine and racemic bupivacaine groups, respectively.

10.5.3 Effect of PCB on uterine and umbilical artery blood flow

In the pilot study the safety of PCB was evaluated by measuring placental site uterine (n=12) and umbilical (n=39) artery blood flow velocity indexes by Doppler ultrasonography before and 15 minutes after PCB. The median of the resistance index (RI) of umbilical artery was 0.57 before PCB and 0.56 15 minutes after PCB in both groups. The mean pulsatility index (PI) of maternal uterine artery was 0.72 and 0.74 before PCB and 0.68 and 0.79 15 minutes after PCB in levobupivacaine and racemic bupivacaine groups, respectively.

10.5.4 Delivery outcome after PCB

In the pilot study, there were 3 operative deliveries (two vacuum extractions and one Caesarean section) among 40 parturients, all in the levobupivacaine group. The indications for operative delivery had no clinical relationship to PCB.

In the randomised study, there were 383 spontaneous vaginal deliveries, 13 vacuum extractions and one Caesarean section among 397 parturients. None of the 14 operative deliveries was associated with a suspected or diagnosed PCB complication.

In the randomised study, the median time from PCB to delivery was 94 minutes (min 10, max 510) in the levobupivacaine group and 90 minutes (min 7, max 395) in the racemic bupivacaine group. Respectively, the median lengths of the second stage of labour were 10 minutes (min 1, max 90) and 13 minutes (min 2, max 105).

10.5.5 Neonatal outcome after PCB

In the pilot study, the median values of cord pH, lactate and base excess after delivery were 7.26, 4.2 mmol/l and -5 mmol/l in the levobupivacaine group and 7.34, 3.8 mmol/l and -5 mmol/l in the racemic bupivacaine group, respectively. Two neonates were taken to the Neonatal Intensive Care Unit (NICU), one because of infection and the other because of wet lung syndrome.

In the randomised study, the median value of cord pH was 7.30 and median base excess was -4 mmol/l in both groups. In the racemic bupivacaine group, two newborns were taken to the NICU, both because of hypoglycaemia.

10.6 Analgesic effect of paracervical block

After exclusion of the cases in which at the 30-min time point after PCB delivery had already taken place, or the cervix was totally dilated and the second stage of labour had begun, 341 parturients with PCB out of 40 + 397 (pilot study + randomised study) remained for analysis of the analgesic effect of PCB.

Figure 6 shows the analgesic effect of PCB measured by means of the VAS (min, max, median, percentiles) at different time points. The difference between VAS values at 5, 15, 30, 45, 60 and 90 minutes after PCB compared with those before PCB was statistically significant ($p < 0.001$). Good pain relief (more than a 50% decrease in the VAS score within 30 minutes) was achieved in 47.2% of the cases. In 23% of cases the pain relief effect was under 20%. Some (12.3%) of the parturients needed subsequent epidural or spinal analgesia because of ineffective PCB.

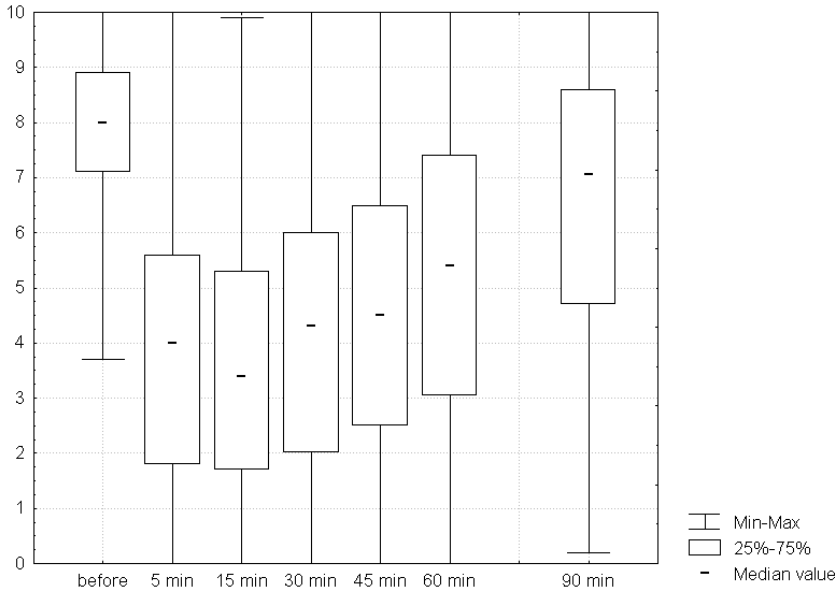


Figure 6 *The analgesic effect of PCB measured by means of a Visual Analogue Scale (VAS) at different time points after PCB and before analgesia. Medians, percentiles, minimum and maximum values are shown. Reprinted from Palomäki O, Huhtala H, Kirkinen P: What determines the analgesic effect of paracervical block? Acta Obstet Gynecol Scand, in press, with permission from Blackwell Publishing.*

10.7 Determinants of good labour analgesia with paracervical block

In study IV, in univariate analysis, significant associations between good pain relief with PCB and primiparity, PCB given by a specialist obstetrician, a high pain score before PCB (> 8) and a long duration of labour were found. A descended presenting part showed a tendency to be associated with better pain relief than a non-descended presenting part, but the data did not reach significance. The level of pain relief was not associated with age of the mother, duration of gravidity, dilatation of the cervix at the time of PCB, number of contractions before PCB, efficacy of the contractions before PCB, induction of labour, analgesic agent (racemic bupivacaine or levobupivacaine), weight or sex of the infant or time of day when PCB was given.

In logistic regression analysis, primiparity, a high pain score before PCB and PCB given by a specialist obstetrician (vs. a resident doctor) were found to be associated with better pain relief 30 minutes after PCB. The statistical data in univariate and multivariate analyses are shown in Table 10.

Table 10 *Determinants of good pain relief in univariate and multivariate analyses in Study IV*

		Univariate analysis		Multivariate analysis		
	n	% of good pain relief	*p*	OR	OR 95% CI	*p*
Parity						
Multipara	226	37		1		
Primipara	115	67	< 0.001	3.06	1.86–5.06	<0.001
Pain score before PCB						
≤ 8	175	39		1		
> 8	166	56	0.002	1.99	1.24–3.19	0.004
Care-giving doctor						
Specialising resident	226	43		1		
Specialised obstetrician	114	57	0.012	1.76	1.07–2.88	0.025

OR = Odds ratio; CI = Confidence interval

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10.8 Inter-observer variation in CTG interpretation

In study V, the level of inter-observer agreement in CTG interpretation was analysed by calculating Pa values for every single doctor's description of CTG readings: baseline, variability, early, variable and late decelerations, uterine tonus, power of contractions, hypertonus and clinical decision on all CTG readings. Agreements regarding clinical decisions were counted separately for junior and senior obstetricians and, to examine the effect of working unit on the decisions, also divided into two groups, the first including the obstetricians from a single large university clinic and the second including obstetricians from 9 delivery clinics of different sizes. The agreements in CTG characterisation and recommendations regarding clinical decision are shown in Table 11.

Table 11 *Agreement between observers in CTG interpretation and clinical operative recommendation given as proportion of agreement (Pa) with 95% confidence intervals (95% CI)*

	Number of observers	Number of CTGs	Pa [95% CI] for normality	Pa [95% CI] for abnormality
Cardiography				
Baseline	31	22	0.79 [0.78-0.80]	0.31 [0.29-0.33]
Variability	31	17	0.73 [0.72-0.74]	0.53 [0.51-0.54]
Early decelerations	31	14	0.66 [0.64-0.67]	0.42 [0.40-0.44]
Variable decelerations	31	14	0.64 [0.63-0.65]	0.52 [0.50-0.53]
Late decelerations	31	14	0.82 [0.81-0.83]	0.33 [0.31-0.36]
Tocography				
Tonus	27	9*)	0.76 [0.75-0.78]	0.18 [0.15-0.20]
Power of contractions	27	9*)	0.24 [0.22-0.26]	0.60 [0.59-0.62]
Hypertonus	29	9*)	0.63 [0.61-0.64]	0.39 [0.36-0.41]
Recommendation for intervention				
All observers	31	22	0.63 [0.62-0.64]	0.55 [0.54-0.56]
Junior obstetricians (≤ 4 years)	16	22	0.62 [0.60-0.64]	0.51 [0.49-0.54]
Senior obstetricians (> 4 years)	15	22	0.64 [0.62-0.67]	0.59 [0.57-0.62]
One single tertiary centre	12	22	0.60 [0.56-0.63]	0.56 [0.53-0.59]
Other delivery clinics	19	22	0.65 [0.63-0.67]	0.55 [0.52-0.57]

*) Only CTG´s with internal tocometry

11 DISCUSSION

Today, the physiology of labouring women remains as it has been throughout the ages. Thus, the goal of modern medicine and obstetrics should be to understand better the mechanisms of contractions and pain and their physiological basis and regulation, and to develop surveillance methods and medication to ensure safety and a less painful labour environment for mother and foetus. The aims of the studies reported in this thesis are set within this research field.

11.1 Methodology

11.1.1 CTG interpretation

Electronic foetal heart rate monitoring by CTG has been used as a common method since the last quarter of the 19th century (Fischer 1973, FIGO 1987). Many guidelines have been published for the interpretation of CTG's to produce standardized and unambiguous definitions of foetal heart rate tracings (FIGO 1987, ACOG 1995, NICHHD 1997). Several studies have shown an association between CTG pathology and foetal acidosis (Low et al. 1999, Hadar et al. 2001, Williams and Galerneau 2003, Sameshima et al. 2004) and perinatal seizures (Thacker et al. 1998, Thacker et al. 2001, Williams and Galerneau 2004). A strict consensus of opinion concerning CTG-classification and clinical intervention in cases of foetal distress suspected on the basis of CTG abnormality is still lacking. However, some signs of CTG pathology raising suspicion of foetal distress are widely accepted. These include absent variability, persistent late decelerations, persistent severe variable decelerations to 70 beats per minute (bpm), lasting for 60 seconds and slowly returning to the FHR baseline, prolonged decelerations (lasting > 2 min), persistent absent variability and bradycardia (< 100 bpm over 4 minutes or < 90 bpm over 3 minutes) (Burke et al. 1989, Shekarloo et al. 1989, Dellinger and Boehm 1995, NICHHD 1997, Huddleston 1999).

In Studies I–IV, the assessment of CTG readings was carried out by the main author to strengthen the validity of the study. In the PCB studies, the main interest was directed to bradycardia, which is easy to diagnose. The assessment of all CTG's by more than one obstetrician would have been practically impossible, because a total of 617 CTG readings were included in the study

material. If two experts had assessed the CTG readings, probably some variation would have emerged. With the method used, the possible misinterpretations of one investigator are likely to distribute equally in both study groups because the sufficiently big study material.

In the present studies dealing with labour augmentation and PCB, the possible abnormalities in CTG potentially caused by the treatment used were evaluated. On the other hand, in the study on tocolysis, normalisation of CTG readings was the main interest in CTG interpretation. As has been shown in former studies and also in Study V, inter-individual disagreement in CTG interpretation occurs widely (Lidegaard et al. 1992, Donker et al. 1993, Bernardes et al. 1997). Thus, use of a rapid classification method in CTG interpretation has been considered essential in standardizing CTG assessments worldwide as regards decision-making in clinical situations and in study arrangements (Cibils 1996).

In some studies, to make interpretation uniform, guidelines have been sent to the obstetricians together with the study material (Ayres-de-Campos et al. 1999). Some guidelines accompanying the CTG data would also have been recommendable in Study V. Another problem concerning Study V is the relatively large proportion of resident obstetricians in the study. On the other hand, residents are the doctors who mainly take care of parturients especially during evening and night times. Thus, perhaps better agreement could have been achieved if all the investigators interpreting the CTG's had been more experienced.

In Study V, our findings were similar to those in a former study (Ayres-de-Campos et al. 1999) in that the proportions of agreement were better for assessments of normality and in cases without recommendation for intervention than in assessments of abnormality and in cases with recommendation for intervention. A natural finding was that the proportion of agreement in the abnormal cases was better among senior obstetricians, whose career was over 4 years, compared with their junior colleagues. Thus, the inter-observer bias was very wide in both groups.

Study V deals with traditional visual CTG interpretation. It is possible that newer techniques such as computerised CTG and STAN analysis would have been more up-to-date study objects. However, visual interpretation still gives the ground to other modern techniques and is used as a screening tool in every delivery unit. These facts led to the decision concerning the nature of the study.

In research studies and also in practical situations such as post-delivery audits the information given about labour can also significantly affect the interpretation of CTG readings. Knowing the neonatal outcome can affect interpretation and also recommendations for intervention. To avoid this kind of bias, only some clinical information concerning pregnancy, maternal diseases and beginning of labour was given with the CTG tracings, with no information about the clinical outcome of the neonate.

Our findings strengthen former findings of wide inter-observer variation and bias and support the production and development of new kinds of foetal

monitoring techniques, and continuous CTG training and audits in every delivery unit.

11.1.2 Technique of PCB

In Studies III and IV, paracervical block was given by means of a modified Kobak´s needle to a depth of 2–4 mm, penetrating the endopelvic fascia to inject the anaesthetic drug into the base of the broad ligament space to interrupt uterine sympathetic afferent activity. The great importance of the depth of injection was first described in a radiological study by Jägerhorn in 1975. Subsequently, many authors dealing with same subject have described a superficial injection technique to a depth of 2–4 mm. There is a little variation in the number of injections; both two (Grenman et al. 1986, Ranta et al. 1995, Nieminen and Puolakka 1997) and four injections (Carlsson et al. 1987, Kaita et al. 2000, Manninen et al. 2000) have been used. Although two studies involving a reduced dose (10 ml of 0.125% bupivacaine) have been published (Carlsson et al. 1987, Nieminen and Puolakka 1997), we used the most common dose, 10 ml of 0.25% levobupivacaine or 0.25% racemic bupivacaine. Because we were already comparing different drugs, adding different doses to the study design would have complicated interpretation.

11.1.3 Assessment of pain experience

The experience of pain is always subjective, and objective measurement of pain is difficult. The most commonly used methods for pain assessment are verbal report methods involving standardized instruments such as the McGill Pain Questionnaire, including a Present Pain Intensity scale (1, mild; 2, discomforting; 3, distressing; 4, horrible; 5, excruciating) and visual scales such as the Visual Analogue Scale (VAS), a 100-mm scale from "no pain" to "pain as bad as it could possibly be" (Lowe 2002).

The advantage of the VAS is its independence of culture, language and intellectual level of the parturient (Stach-Lempinen et al. 2001). A criticism is that an extremely complex multidivisional phenomenon like labour pain is reduced to a single quantitative dimension of intensity. The capability of the subjects may be restricted because of medication. The interpretation of maximal pain is also dependent on past experience, personality and, in pregnant subjects, parity (Lowe 2002).

In spite of criticism of the VAS, in Study IV we preferred it to other descriptive pain scales because it is step-less and thus offers a better tool to score pain than other methods. Because there was a relatively wide scale in the interpretation of the pain experience before pain relief, we chose to measure the percentage decrease in pain score 30 minutes after PCB. Thus the later pain score was always compared with the pre-analgesia score reported by the same

parturient, making it possible to eliminate the effect of different maximal pain scaling of parturients.

11.1.4 Statistical methods

In many studies on inter-observer variation, kappa statistics are used. The result of kappa statistics is dependent on the frequency of each category used, and its usefulness in measurement of inter-observer variation of categorial assessments is limited. A new method, the proportion of agreement method, with 95% confidence intervals to measure inter-observer variation in categorial variables, was introduced by Grant in The Lancet in 1991.

The advantage of the proportion of agreement method is that agreements concerning assessments of abnormality and normality are counted separately. In Study V, agreement concerning normal and abnormal tracings as well as recommendations for intervention or no intervention could be counted separately by using this method. The clinical importance of this method in the case of CTG interpretation is that disagreement regarding normal tracings can lead to unnecessary operative intervention and disagreement in abnormal cases may lead to poor neonatal outcome.

11.2 Mode of delivery among the study subjects

The actual mode of delivery in Studies I–V is shown in Table 12.

Table 12 *Mode of delivery in Studies I–V*

Study	Study group	Spontaneous Vaginal (%)	Operative Vaginal (%)	Caesarean Section (%)
I	Propranolol	73	16	11
	Placebo	85	11	4
II	Tocolysis effective	24	10	65
	Tocolysis ineffective	4	21	75
III	Levobupivacaine	97	3	0
	Racemic bupivacaine	96	3.5	0.5
IV		95	3.5	0.5
V		41	23	36

The overall frequencies of mode of delivery in our hospital during the study period were 78–80% for spontaneous vaginal deliveries, 7% for operative vaginal deliveries (mostly vacuum extractions) and 13–15% for Caesarean sections.

Reflecting these figures, the mode of delivery in Study I was similar to that in the whole population delivering in our hospital. Because subject selection took place with strict criteria for arrest, our results point to the fact that in most cases dysfunctional labour can lead to spontaneous delivery.

In Studies II and V the operative delivery rates differed significantly from that of the general population, reflecting the severity of the labour problem among these parturients. In Study II all labours were complicated by severe CTG pathology, and in Study V the cases were selected to represent more pathological courses of labour than in the general population.

In contrast to Studies II and V, Studies III and IV represent a population with few intra-labour complications and a high percentage of spontaneous vaginal deliveries.

11.3 Modulation of uterine contractions during delivery

11.3.1 Treatment of hypocontractility

Abnormalities in uterine contractile activity are leading causes of acute Caesarean section in many countries (O'Driscoll et al. 1984, ACOG 2003). The increased morbidity connected to acute CS includes haemorrhage, thrombo-embolic diseases, infections, placental problems and ectopic pregnancies (Hemminki and Meriläinen 1996, Jackson and Paterson-Brown 2001, Häger et al. 2004) and has led obstetricians to carry out research into the prevention of labour disorders caused by uterine hypo- or hypercontractility.

The most commonly used medication is oxytocin, given as an infusion, which can shorten the duration of labour. In one randomised trial with 694 primiparas a significant reduction in CS rate was shown by means of augmentation of labour with oxytocin (Pattinson et al. 2003). However, in most studies evidence of a consistent reduction in CS rate with the use of oxytocin is lacking (Frigoletto et al. 1995, Thornton 1997, Sadler et al. 2000, ACOG 2003). Some other treatments such as use of prostaglandin E_2 vaginal gel (Oppenheimer et al. 2005) or labouring in water (Cluett et al. 2004) have been studied in connection with management of dystocia. A single 1 mg dose of PgE_2 vaginal gel has been found to be more effective than placebo in resolving dystocia. It was not associated with uterine hyperstimulation. There was an unexpected and unexplained increase in the incidence of second stage CS because of dystocia in the PgE_2 group, and because of this, further investigation is needed before practical use of this treatment (Oppenheimer et al. 2005). In a randomised

controlled trial of labouring in water versus augmentation (amniotomy and oxytocin) no differences in rates of operative delivery were found between the groups (Cluett et al. 2004).

In the 1960's some small studies on contractility of the human uterus in connection with drugs influencing β-adrenergic receptors were published, showing the potential of propranolol to reverse the inhibitory effect of the β-agonist isoproterenol on human uterine motility, to increase uterine activity in pregnant and non-pregnant subjects and increase uterine activity during uncomplicated labour (Mahon et al. 1967, Wansbrough et al. 1968, Barden and Stander 1969). The first non-controlled study on the use of propranolol in dysfunctional labour was carried out in 1975 (Mitrani et al. 1975).

In the first and only former randomised, placebo-controlled study, Sanchez-Ramos *et al.* (1996) found a reduction of 50% in the CS rate when using propranolol combined with oxytocin in the treatment of labour dystocia. In Study I, the study arrangement was similar to that in this former study, but no reduction in CS rate was found in our study.

An explanation for this difference might be differences in basic CS rate in the study hospitals. In the former study the CS rate was not mentioned, but it can be supposed to be high, because 26.5% of the parturients in the propranolol group and 51.1% in the placebo group ended up undergoing CS. The operation policy in our clinic has been relatively conservative and expectant, with an overall CS rate of 14%. We also have commonly used intrauterine pressure measurement to avoid acute Caesarean sections resulting from dystocia, and the personnel of the delivery room are used to interpretation of the tocometric part of CTG, and the use of necessary dosage augmentation. This could also partly explain the low operative frequency in our study material. Again, our data did not even show a trend towards a lower CS rate in the propranolol group, which does not favour the view that increasing the sample size would show a reduction in operation rate.

Another explanation for different findings in the two studies could be different categorization of labour disorders. This is always subjective and could lead to different interpretations among obstetricians and clinics.

In advanced labour the power of contractions, measured by intrauterine pressure catheter, should rise to 160–300 Montevideo units (Caldeyro-Barcia and Poseiro 1959, Burnhill et al. 1962, Hauth et al. 1986). In our study, all parturients had an intrauterine pressure measurement catheter inserted before administration of study drug, and the median power of contractions before augmentation was 80 and 93 Montevideo units in the propranolol and placebo groups, respectively, which suggests successful subject selection. According to Sanchez-Ramos *et al.*, 49% of the parturients in the propranolol group and 55% in the placebo group in their study had adequate patterns of uterine contractility (at least three contractions in 10 minutes at a power of at least 150 Montevideo units) at the start of the study, and only 46 cases had inadequate uterine contractility. Among the subjects with adequate uterine contractility the frequency of CS was similar between the groups, and among the cases with primary inadequate contractility a lower CS frequency was found in the

propranolol group. It is probable that those 50 cases (more than half of the study population) with adequate contractility at the beginning of the study had some other reason than hypocontractility for labour arrest, and the sample size of the rest of the material was too small to draw conclusions about the effect on CS frequency.

Another basic difference between these two studies (Study I and the one by Sanchez-Ramos *et al*.) is the timing of CS. In the study by Sanchez-Ramos *et al.*, Caesarean section was performed if there was no response to the second dose of study drug, i.e. within two hours of the beginning of oxytocin and propranolol/placebo. In our study, treatment after the study drug(s) was more expectant and led to spontaneous labour in most cases. Our policy is also supported by a recent finding that cases of oxytocin-augmented labour proceed at slower rates than spontaneous labours and in these cases CS should not be carried out after two hours' arrest of labour (Rouse et al. 2001).

According to our findings, propranolol combined with oxytocin does not affect the CS rate, but confers a mild benefit to the progress of dysfunctional labour without a risk of CTG pathology or neonatal adverse outcome. No differences were found between the neonatal groups in cord blood biochemical test results, blood pressure, pulse frequency, breath frequency, blood glucose levels or need of NICU care, these findings consequently pointing to the conclusion of improbability of propranolol-related neonatal problems. A new and interesting study field could be the use of propranolol alone for augmentation. According to our findings on safety, this kind of study should be possible in the future. However, the potentially slower metabolism in neonates has to be remembered. In our small material we found a higher drug concentration in neonates after a 4 mg propranolol dose, although in parturients the concentrations after doses of 2 mg and 4 mg were similar. Close monitoring of neonates after exposure to a β-blocking agent is important, as well as remembering the contraindications for this kind of medication among patients with chronic illnesses such as bronchial asthma, symptomatic bradycardia or AV conduction deficiency, and in cases with diminished foetal reserves. Thus, in many cases amniotomy and oxytocin augmentation are sufficient for adequate progress of labour.

11.3.2 Treatment of uterine hypertonus

Pathological CTG readings are often but not always a consequence of spontaneous or iatrogenic hypercontractility of the uterus. This kind of labour pathology can be missed without the use of an intrauterine pressure measurement device. In our studies, we used an intrauterine pressure measurement device. A specific treatment of hypercontractility, and also a well-defined and recommended treatment of non-reassuring CTG findings with or without marks of uterine hypertonus, is tocolytic therapy with β-mimetics, nitroglycerin or, according to the results of a recent randomised trial, the oxytocin antagonist

atosiban. In former studies on the subject and also in Study II, a randomised placebo-controlled study is impossible to carry out for ethical reasons.

In spite of the retrospective setting of Study II, it can be assumed that most of the pathological CTG readings would have continued, leading to acute CS without tocolytic therapy. Thus the study, even without control material, truly revealed the effect of acute tocolysis on CTG abnormality. In 67% of cases, tocolysis effectively normalised the CTG pattern. In addition, pathological foetal blood pH values improved in the majority of cases after tocolysis. Among the cases with normalised CTG patterns the diminishing of Montevideo units in intrauterine pressure measurement and improvement of signs of hypertonicity of the uterus were significantly more common than in the group in which the CTG pattern did not improve. On the other hand, good CTG responses to tocolytic therapy were also common in cases without uterine hypertonicity, which may be a result of improved uteroplacental blood circulation after tocolysis or some other, as yet unknown effect on the foetus or intrauterine environment. Beta-mimetic agents have been shown to increase myometrial blood flow, but not change the intervillous and umbilical vein flow (Kauppila et al. 1978, Jouppila et al. 1985). Maybe also some other still unknown metabolic changes may occur after administration of a β-mimetic agent and alleviate acute foetal distress.

Positive effects of emergency tocolysis with various agents on CTG patterns and pH values have also been established in several former investigations (Ingemarsson et al. 1981, Gummerus 1982, Burke et al. 1989, Kulier et al. 1997, Kulier and Hofmeyr 2000).

In a study with 553 parturients whose foetuses had pathological CTG patterns and intrapartum foetal acidosis (pH < 7.25) diagnosed by scalp blood sampling, β-mimetic intravenous therapy improved the pH by 0.05 or more in 72.8% of cases. The recovery rate was found to be independent of the degree of inhibition of uterine activity (Cabero et al. 1988).

In Study II we found that no single clinical parameter can directly be used to select cases for tocolytic therapy or identify cases in which the CTG pattern will remain severely pathological. Because tocolysis was not associated with any significant side-effects, it seems to be worth trying before any definitive decision on emergency operative delivery.

The American College of Obstetricians and Gynecologists (ACOG) recommends in a guideline the use of intrauterine resuscitation tools such as discontinuation of oxytocin, initial left lateral recumbent positioning followed by right lateral or knee-elbow positioning if necessary, maternal oxygen administration, rapid intravenous infusion of non-glucose crystalloid, treatment of hypotension if needed, inhibition of uterine contractions by tocolytic therapy and consideration of amnio-infusion before acute Caesarean section (ACOG 1995).

Before the first report on atosiban for acute tocolysis (Afschar et al. 2004), the most commonly used drugs for intrapartal tocolysis have been β-mimetics (ritodrine, terbutaline, fenoterol, bufenine and hexoprenaline) (Gerris et al. 1980, Caritis et al. 1985, Shekarloo et al. 1989, Kulier and Hofmeyr 2000), as in our study also.

Nitroglycerin has also been used as a tocolytic agent during delivery (Axemo et al. 1998, Smith and Brien 1998). The superiority of terbutaline over magnesium sulphate in acute tocolysis has been shown (Magann et al. 1993), but up to now there have been no comparative studies between β-mimetics and nitroglycerin in acute tocolysis.

Compliance with ACOG recommendations in cases of CS for foetal distress has been studied in one retrospective study and as a review of the literature. In the review only three reports out of 169 articles provided data on the use of tocolytics for intrauterine resuscitation. In these studies tocolysis had been used in 16% of cases. The authors conclude that ACOG guidelines seem to be difficult to assess by physicians and incomplete compliance is common (Chauhan 2003). In a retrospective chart review in one tertiary centre tocolytic agents had been used before acute CS because of non-reassuring FHR patterns in 25% of cases (Hendrix et al. 2000). In a study on maternity care professionals (obstetricians, midwives and anaesthetists) concerning potential treatments during acute intrapartum hypoxia, Kinsella and Thurlow (2000) found that only 24% of professionals could name two or three factors besides maternal oxygenation which might be manipulated to alter foetal oxygen levels.

In Study II there was a lower proportion of operative deliveries and emergency Caesarean sections in the group in which tocolysis was effective. The infants in this group had a significantly better base excess in cord blood samples and a tendency to have better 1- and 5-minute Apgar scores and cord blood pH. The therapy did not increase peripartal bleeding, and blood loss was comparable to ordinary blood loss in vaginal delivery and Caesarean section.

According to the findings in Study II and the results of former studies on acute tocolysis for foetal distress, it can be stated that tocolysis is harmless and in the majority of cases it appears to give to the obstetrician important additional time for making decisions without increasing foetal risk. If tocolysis is effective, normal progress of labour and vaginal delivery are possible in some cases, because after discontinuation of tocolysis the contractions reach their former power rapidly. On the other hand, in the cases in which CS is necessary, by using tocolytic therapy it is possible to repair the patient properly for the operation.

11.4 Safety and applicability of paracervical block

Although epidural and spinal analgesia are unquestionably the leading methods for pain relief in labour, there still exists a need for an alternative birthing environment in which a broad spectrum of non-pharmacological and pharmacological approaches to pain relief are used (Thorp and Murphy-Dellos 1998, Lowe 2002). Thus, much attention has been paid to better understanding of labour pain and its management (Caton et al. 2002). In some cases reasons such as contraindications for regional analgesia or resource problems in a delivery unit can lead to the need for additional alternative pain relief methods such as PCB.

On the other hand, concerns about the safety of some pain relief methods, including PCB, have highlighted the need for additional safety studies. Recently, the need for studies on PCB with sufficient subjects and well-defined techniques and outcome measures has been emphasized (Caton et al. 2002, Rosen 2002).

Our study on 440 PCB´s in 397 labours was directed to answering some safety questions regarding this topic. According to our findings in Study III, PCB was not associated with foetal or neonatal hypoxia, neonatal outcome was good in every case, and no admission to a Neonatal Intensive Care Unit was needed as a result of hypoxic or any other complication associated with labour analgesia. The rate of operative deliveries was low after PCB. The low incidence of transient post-PCB bradycardia (total 3.2%; in the levobupivacaine group 2.6% and in the racemic bupivacaine group 3.8%) justifies the belief that PCB in experienced hands has a place as an alternative pain relief method in modern obstetrics.

The hypothesis of less CTG pathology and better outcome after PCB with levobupivacaine compared with racemic bupivacaine was not true in our material. We found no significant differences between the racemic bupivacaine and levobupivacaine groups in CTG pathology, neonatal outcome, power of contractions or manner of delivery. Again, the analgesic effect of levobupivacaine was equal to that of racemic bupivacaine, and taking into account the former findings of lower CNS and cardiovascular toxicity of levobupivacaine compared with racemic bupivacaine, according to our findings levobupivacaine could safely be taken into practical use in PCB, as it already has in intrathecal and epidural analgesia.

In our study, a superficial injection technique and low concentrations (0.25%) of bupivacaine were used. Probably, the prompt injection technique enabled us as well as some former investigators using a similar injection technique (Meis et al. 1978, Jägerhorn 1975, Carlsson et al. 1987, Ranta et al. 1995) to show even lower bradycardia rates (2.6 and 3.8%) than have been reported after intrathecal labour analgesia (5–7.7%) (Palmer et al. 1999, Mardirosoff et al. 2002).

An interesting field for further studies would be to investigate maternal and foetal haemodynamics after PCB by Doppler ultrasonography. The results of our pilot study showed no vasoconstriction in the umbilical or maternal uterine artery during PCB. Manninen *et al.* (2000) found an increase of PI, indicating an increase in vascular resistance, in the maternal uterine artery after PCB, PI values in the maternal femoral, foetal umbilical and foetal middle cerebral arteries being unchanged. In a small study by Räsänen and Jouppila (1994), a marked increase of umbilical artery PI and a minor increase in maternal uterine artery PI was found in cases of foetal bradycardia after PCB, these findings pointing to the fact that vasoconstriction would be the probable explanation for the development of bradycardia. In this study no signs of vasoconstriction in the umbilical artery or maternal uterine artery after PCB were found in pregnancies without signs of chronic or acute foetal distress.

According to our findings, PCB does not negatively affect labour contractions. Among the 52 cases in which intrauterine pressure measurement data was available, an increase in uterine activity after PCB was found. Among

these subjects there were three cases of post-PCB bradycardia, with a 30-Montevideo unit rise in uterine activity. In other studies, controversial findings have been reported concerning the effect of PCB on contractions. In a study on 32 women receiving PCB with 25 mg racemic bupivacaine, a slight decrease in uterine activity after PCB was found, but clinical progress seemed to remain normal (Read and Miller 1979). In another study involving 60 women receiving PCB with 25 mg or 50 mg of racemic bupivacaine, an increase in uterine activity of 100 Montevideo units was found in 11 out of 14 cases in which post-PCB bradycardia developed (Achiron et al. 1987).

In contrast to the situation concerning epidural analgesia, which has been found to be associated with longer labour and a higher rate of instrumental vaginal delivery (Lieberman and O'Donoghue 2002), we found a low incidence of operative deliveries in our study population. The finding was similar to those in other PCB studies (Carlsson et al. 1987, Ranta et al. 1995), reflecting successful selection of parturients whose progress of labour had been normal until the point of pain relief and whose dilatation was presumed to be progressing rapidly. The progress of labour as well as the length of the second stage was also found to remain normal after PCB among our parturients. Out of 437 subjects, a VAS value at 30 minutes after PCB was not available in 96 cases for the analyses in Study IV. This finding reflects very rapid dilatation in 22% of the study population, these parturients being already in the second stage of labour or having already delivered 30 minutes after PCB. This group of women could have missed pain relief if a more time-consuming procedure such as epidural analgesia had been chosen for pain relief.

The range of analgesic effect of PCB was wide and its mean efficacy was found to be moderate in the whole study material. In Study V the mean VAS score 30 minutes after PCB was 4.3; in other studies values between 4.6 and 5.0 have been found (Grenman et al. 1986, Ranta et al. 1995, Nieminen and Puolakka 1997). In Study IV, associations between good pain relief with PCB and primiparity, a specialist obstetrician as the care-giving doctor and a high pain score (> 8) before PCB were found.

The effect of the experience of the obstetrician is easy to understand and has also been shown by other authors. In a study by Saloheimo (1968) with 500 PCB´s, the failure rate of anaesthesia was 17.4% for residents and 8.4% for specialist obstetricians. In our study pain relief was also better among the parturients who experienced more intensive pain before analgesia.

Although it has been shown that parous women have a higher pain threshold (Hapidou and DeCatanzaro 1992) and that primiparas experience greater pain during the first stage of labour, whereas multiparas experience more pain during the second stage of labour (Lowe 1987, Ranta et al. 1996, Sheiner et al. 1998, Lowe 2002), our finding concerning the good pain relief effect of PCB among primiparas has not been published before. The finding can be explained by understanding the physiological basis of labour pain. Among multiparas the first stage of labour is shorter and labour is characterized by sudden descent of the presenting part, producing distension and traction on pelvic structures and intense somatic pain at the end of the first stage and during the second stage of

labour. These stimuli are transmitted via the pudendal nerve though the anterior rami of S2 though S4, and cannot be blocked by PCB. In contrast, among primiparas the predominating pain is visceral, arising from mechanical distension of the lower uterine segment and cervical dilatation and is transmitted to the posterior nerve root ganglia at T10 through L1 (Lowe 2002).

12 CONCLUSIONS

1. In arrested labour, 2 mg of intravenous propranolol combined with oxytocin vs. placebo plus oxytocin shortens the augmented part of labour but does not affect the CS rate. Propranolol appears to be safe for neonates and does not result in pathological CTG readings.

2. Tocolysis with the β-mimetic agents ritodrine hydrochloride or bufenine hydrochloride is an effective method to normalise pathological CTG patterns during the first stage of labour, even in cases without uterine hypertonus.

3. Paracervical block is a safe pain relief method for low-risk parturients. The rate of foetal bradycardia is low after PCB. Levobupivacaine and racemic bupivacaine in PCB did not differ as regards CTG pathology, pain relief effect, neonatal outcome or labour course after PCB.

4. The analgesic effect of PCB is wide in range. Primiparas benefit more than multiparas from PCB, as assessed by VAS. The best pain relief after PCB is achieved among primiparas. Good pain relief is also connected with an experienced obstetrician giving the block and with a high pain score before PCB.

5. Inter-observer variation in the interpretation of CTG readings and recommendations for intervention is wider in abnormal cases than in normal cases. To improve the reliability of CTG, uniform classification and standardized training in CTG interpretation are needed, and increased use of computerized CTG is recommended.

13 ACKNOWLEDGEMENTS

I wish to express my gratitude to:

Professor and supervisor Pertti Kirkinen, Head of the Department of Obstetrics and Gynaecology of Tampere University Hospital, for positive attitude, encouragement and practical help during study years.

Supervisor, Docent Risto Tuimala, who suggested part of the themes for investigation and patiently supported me throughout the study. From the very beginning of my working period in Tampere University Hospital he has been the human, warm heart of the clinic and also a promotor for many social activities among collegues.

Official reviewers of this thesis, Docent Ulla Ekblad and Docent Jukka Puolakka, for conscientious review and valuable advice and criticism on the manuscript.

Co-authors MSc. Heini Huhtala and MSc. Tiina Luukkaala for qualified and patient help with the statistical part of the work, M.D., Ph.D. Jukka Uotila for support and friendship during the study years, Docent Outi Tammela for paediatric expertise, for M.D. Miia Jansson and Medical Student Riikka Luoto for practical help with collecting study material and M.D., Ph.D. Timo Kaila and Research Associate Merja Lavapuro for their contribution in the propranolol study.

Dr. Nicholas Bolton for skillful linguistic corrections of the original publications and this dissertation and for his flexible and fast responses to my requests during the study period.

Mrs. Eva-Liisa Saaristo, midwife, who friendly and skilfully assisted me with practical work during the material collection in the delivery room.

Special nice collegues and friends constituting Kenttävartio Ahma; my all Ahma-children, especially A, AA, B, C, Fas and Pentu, Ahma-grandmother Kirsti and all other Ahmas, with whom I have shared so many expressing, fun and relaxing moments spending freetime together in Finland and also abroad.

All present and former colleagues at the Department of Obstetrics and Gynecology in Tampere University Hospital for collegial support during the study.

All midwifes in the delivery room in Tampere University Hospital for help during the material collection and excellent fellowship during all past years. It is a pleasure for me to work with you.

The staff of postnatal departments and neonatal intensive care unit in Tampere University Hospital for help during the propranolol study and the personnel of the Medical Library and the Department of Medical Records in Tampere University Hospital for practical and reliable help with the study material.

Helena and Timo Porkkala, Marjo Kuortti, Minna Kaura-Mattila, Jouni Mattila, Meri and Antti Koivuniemi and all other lovely friends of mine and our family, who have given me support during the scientific work and who shared friendship, conversations and social affinity with me. It has given me much power for going on with the study.

My dear mother Hilkka-Liisa Palomäki and dear, late father Aimo Palomäki for all love and care throughout my life and positive, trusting attitude towards my intentions in scientific, cultural and many other fields of life, and on the part of my mother, also for all practical help with loving care of my children during the study period.

My world´s best, dear sister Anne Jyrkiäinen for sharing many aspects of my life and for always positive support and also world´s best, dear brother Ari Palomäki, who was a forerunner in our family with scientific work, for many practical advice and good conversations over the study field during my work.

The families of my sister and brother, Paavo, Senni, Mari and Juho Jyrkiäinen and Annamari, Annika, Erika ja Aaro Palomäki, for giving me and my family a stabile, loving context of life and a lot of joy with relatives.

My deepest gratitude is due to my dear husband Markku Huhtala and our dear daughters Taija and Tinja Huhtala for sharing the everyday life with me and for encouragement and positive attitude towards my scientific aims even during the times, when those aims did affect on our family life.

All the women who took part in the studies and all the colleagues who took part in the study V by interpreting the CTG readings.

Grants from the Medical Research Fund of Tampere University Hospital, Tampere University, Finnish Gynecological Association and the Pirkanmaa Regional Fund of the Finnish Cultural Foundation for the financial support.

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15 ORIGINAL COMMUNICATIONS