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# FETAL SURVEILLANCE AND OUTCOME IN POSTTERM PREGNANCY

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## **Academic Dissertation**

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**Faculty Opponent:** Professor Philip J Steer, London, United Kingdom

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Abstract  To minimize the risk of short-term and long-term morbidity and mortality among children born postterm, studies were performed to evaluate the fetal surveillance program.  (1) Male-fetus pregnancies were at an increased risk for induction of labor postdate, when recognized as postterm according to the early pregnancy ultrasound dating, but the difference disappeared after adjustment for the gender-dependent size difference at dating; (2) Newborn girls tended to have low Apgar scores more often than boys since they were judged postterm later; (3) A lower rate of meconium stained amniotic fluid was the only potential benefit by starting intensified fetal surveillance 1-3 days prior to the postterm period, but neonatal meconium aspiration was rare (3/1000) and not related to a later start; (4) Solely due to the early neonatal mortality, the total mortality in postdate/postterm pregnancies was higher than among children born at term; (5) In a long-term perspective, morbidity – in practically all organ systems - tended to be lower among children born postdate/postterm compared with children born at term; (6) Fetal brain-sparing flow, as a sign of chronic hypoxemia, was not associated with an impaired outcome, either in the short-term or long-term perspective; (7) Umbilical cord arterial blood pH decreases linearly with gestational age from 37 to 42+ weeks; (8) In comparison with a stationary cutoff of pH at 7.10 to indicate acidemia, a gestational age-adjusted reference range of mean $\pm$ 2 SD results in 25 % fewer diagnoses of acidemia in term newborns and 35 % in postterm newborns.		
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# FETAL SURVEILLANCE AND OUTCOME IN POSTTERM PREGNANCY

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LUND UNIVERSITY

Malmö 2007

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*‘The roots of knowledge are bitter,  
but its fruits are sweet’*

*Cicero (106 BC – 43 BC)*



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## **LIST OF PAPERS**

This Ph.D. thesis is based on the following papers, which will be referred to by their Roman numerals.

- I** Laczna Kitlinski M, Källén K, Marsál K, Olofsson P.  
Skewed fetal gender distribution in prolonged pregnancy: a fallacy with consequences.  
*Ultrasound in Obstetrics and Gynecology* 2003;21:262-6.
- II** Laczna Kitlinski M, Molin J, Källén K, Olofsson P.  
Starting fetal surveillance earlier in postterm pregnancy - a 15-year quasi-randomized controlled study.  
(Submitted)
- III** Laczna Kitlinski M, Källén K, Olofsson P.  
Fetal surveillance in postterm pregnancy: The contribution of middle cerebral artery Doppler flow velocimetry.  
(Submitted)
- IV** Laczna Kitlinski M, Källén K, Marsál K, Olofsson P.  
Gestational age-dependent reference values for pH in umbilical cord arterial blood at term.  
*Obstetrics & Gynecology* 2003;102:338-45.

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## ABBREVIATIONS

AC	abdominal circumference
AD	abdominal diameter
AFI	amniotic fluid index
AGA	appropriate-for-gestational-age
BFC	blood flow class
BPD	biparietal diameter
BPP	biophysical profile
BSF	brain-sparing flow
CBF	cerebral blood flow
CI	confidence interval
CPAP	continuous positive airway pressure
CPR	cerebro-placental ratio
CRL	crown-rump-length
CS	cesarean section
CST	contraction stress test
CTG	cardiotocography
EDD	expected day of delivery
FHR	fetal heart rate
FL	femur length
FVW	flow velocity waveform
GA	gestational age
HIE	hypoxic ischemic encephalopathy
IOL	induction of labor
IUFD	intrauterine fetal death
IUGR	intrauterine growth restriction
LGA	large-for-gestational-age
LMP	last menstrual period
MAS	meconium aspiration syndrome
MCA	middle cerebral artery
NICU	neonatal intensive care unit
NST	nonstress test
NT	nuchal translucency
OCT	oxytocin challenge test
OD	odds ratio
ODFD	operative delivery for fetal distress
ODFP	operative delivery for failure to progress
PI	pulsatility index
SD	standard deviation
SGA	small-for-gestational-age
UA	umbilical artery
UAS	uterine artery score
WD	weight deviation

## INTRODUCTION

### HISTORY

The issues of postterm pregnancy, its risks, and its management options have generated considerable discussion for more than a hundred years and are still a matter of controversy. The problem was described in modern obstetric terms for the first time in 1902 by Ballantyne, who wrote: ‘The postmature infant ... has stayed too long in intrauterine surroundings; he has remained so long in utero that his difficulty is to be born with safety to himself and to his mother. The problem of the ... postmature infant is intranatal’.

For many years the biological possibility that a pregnancy could exceed the 42<sup>nd</sup> week was questioned. It was not until the early 1960s that conclusive evidence of an increased risk of fetal mortality in postterm pregnancy was presented [McClure-Browne, 1963]. Many obstetricians met this information with criticism. However, postterm pregnancy was gradually recognized as a problem when the pediatricians became interested in the matter. In 1954, in a postmature classification system, Clifford described the degree of affliction suffered by postterm neonates, and eventually in the late 1960s and 1970s, with the advent of ultrasound dating, the fetal risk associated with postterm pregnancy was fully established.

### EPIDEMIOLOGY

The reported incidence of postterm delivery has ranged from 2 to 14 % [Beischer *et al.*, 1969; Grennert *et al.*, 1978; Tunon *et al.*, 1996; Ingemarsson & Källén, 1997]. The variation in the presented figures can be due to differences in definitions of postterm delivery [Shea *et al.*, 1998], in policies of induction of labor (IOL) [Shipp *et al.*, 2001], in pregnancy dating, and in ethnicity. Also, it is common in the literature that authors falsely refer to postdate pregnancies as postterm before a gestational age (GA) of 294 days is completed. About 98 % of all pregnancies in Sweden are dated by ultrasound in the late first trimester or early second trimester, which gives an incidence of prolonged pregnancy of 2-3 % [Grennert *et al.*, 1978; Ingemarsson & Hedén, 1989]. However, national data for the period 1982-1991

showed a prevalence of 7.7 % [Ingemarsson, 2000]. An ultrasound scanning quality below the standard might be one reason for this unexpectedly high incidence. The incidence is higher in primiparous, obese, and smoking women [Hovi *et al.*, 2006].

Traditionally, the expected day of delivery (EDD) has been calculated by using Naegele's rule [Naegele, 1836], with the assumption that a pregnancy lasts for 280 days from the start of the last menstrual period (LMP) to EDD. However, use of LMP as a determinant of gestational age has a limited reliability, since it applies only to women with regular menstrual cycles, i.e., with ovulation on cycle day 14. Moreover, 30-40 % of women cannot recall the exact date of the first day of their LMP [Geirsson, 1991]. Use of LMP as a determinant of gestational age will result in a falsely high reported incidence of postterm pregnancy. Gardosi and colleagues reported a postterm delivery rate of 9.5 % among women dated by LMP, but a rate of 1.5 % if ultrasound dating was used [Gardosi *et al.*, 1997]. Several studies have confirmed a decrease to 2-5 % with use of ultrasound dating in the early second trimester [Grennert *et al.*, 1978; Boyd *et al.*, 1988; Tunon *et al.*, 1996; Taipale *et al.*, 2001].

It is not known what factors trigger the endocrine cascade of events leading to the onset of parturition, and the reason why a pregnancy becomes postterm is not completely understood. Conditions such as placental sulfatase deficiency, fetal anencephaly, absence of the fetal pituitary gland, and fetal adrenal hypoplasia all have in common that the usually high concentrations of maternal estrogen are low and that the pregnancy often continues beyond term [Cunningham *et al.*, 1989a].

A number of other factors such as high maternal age, low educational level, exposure to aspirin, alcohol consumption, and smoking, have been found to be associated with prolonged pregnancy. The most consistent predictor is a previous prolonged pregnancy [Bakketeig *et al.*, 1979; Mogren *et al.*, 1999; Olesen *et al.*, 1999], although prolonged pregnancy is more common in nulliparous women [Eden *et al.*, 1987a; Mittendorf *et al.*, 1993]. Some studies have shown an increased incidence in association with maternal obesity [Johnson *et al.*, 1992] and pregnancy with a male fetus [Divon *et al.*, 2002; Kitlinski *et al.*, 2003]. Ethnic differences play a role, with a higher incidence in the white race compared with the black race [Papiernik *et al.*, 1990; Mittendorf *et al.*, 1993].

The relative risk of recurrence of postterm delivery is about 2 to 2.6 [Olesen *et al.*, 2003], with an increase to 3.2 if the woman has had two previous prolonged pregnancies [Shipp *et al.*, 2001]. Olesen and colleagues [2003] reported a reduced risk of recurrence of postterm delivery after a change of partner. Laursen *et al.* [2004] examined same-sex twin pairs and concluded that maternal genes influence the chance of having a postterm pregnancy; no paternal genetic influence was found.

## **ESTIMATION OF GESTATIONAL AGE**

### ***Dating by the last menstrual period***

As mentioned above the traditional way to calculate the EDD has been by Naegele's rule [Naegele, 1836]. This is done by adding 9 months and 7 days to the date of the first day of the LMP, or by reducing 3 months and adding one year and 7 days, with the assumption that a pregnancy lasts 280 days. This now old-fashioned method is associated with considerable uncertainty on account of the major variations in menstrual cycle length [Harlow & Ephross, 1995]. Many women, especially those with long menstrual cycles, have difficulties in recalling their LMP. This can lead to an overestimation of GA compared with ultrasound [Campbell *et al.*, 1985].

### ***Dating by ultrasound fetometry***

All fetuses of the same GA do not have the same size. There is a difference in size between male and female fetuses already in early pregnancy, and between fetuses with different ethnic backgrounds. This biological variation is very small and many authors claim that it can be ignored. In Malmö, the average length of gestation is 279.6 days in female fetus pregnancies and 280.4 days in male fetus pregnancies [Weldner, 1998]. Studies of in-vitro fertilized conceptions indicate very good agreement between ultrasound dating and the true gestational age [Geirsson & Have, 1993].

### **First trimester dating**

Since dating by the menstrual history is unreliable, accurate dating with ultrasound has become a cornerstone in obstetric management. The gestational sac is visible by vaginal ultrasound from about 4.5 weeks and can be correlated to GA

[Robinson, 1975; Warren *et al.*, 1989; Daya, 1991]. Measurements of the crown-rump-length (CRL) in weeks 5-12 are the most accurate method of determining GA in the first trimester [Selbing, 1983; Wisser *et al.*, 1994; Tunón *et al.*, 2000]. In addition to dating, an ultrasound examination in this period provides important information about fetal viability, chorionicity in twins, placental localization, and to some degree also about fetal malformations.

In addition to the good accuracy of dating by a first trimester ultrasound scan, another advantage of early scans is the possibility of performing nuchal translucency (NT) measurements, as a tool for screening for Down syndrome and other abnormalities at 12-14 gestational weeks [Nicolaidis, 2005; Saltvedt *et al.*, 2006].

### **Second trimester dating**

When the CRL is more than 60 mm, measurements of the fetal biparietal diameter (BPD), femur length (FL) and abdominal circumference (AC) or abdominal diameter (AD) are more accurate for dating. BPD and FL are used in routine measurements for estimation of gestational age between 15 and 22 weeks [Persson & Weldner, 1986; Geirsson & Have, 1993]. Particularly important when performing routine ultrasound examination in the second trimester is to scan for fetal malformations, which are best detected in this period. Ultrasound estimation of the gestational length is based on a standard growth curve and is not recommended after 20 completed weeks, as the variation in fetal growth increases after that time.

### ***Fetal gender differences in size at ultrasound dating***

It is well known that by the time of ultrasound dating in the early second trimester, male fetuses are already larger than females. Male fetuses may thus be assigned a falsely longer gestational age and female fetuses a falsely shorter [Tunón *et al.*, 1998]. Many investigators [Pedersen, 1980; Wald *et al.*, 1986; Moore *et al.*, 1988], but not all [Selbing & McKay, 1985], have found that the BPD of male fetuses is larger than that of female fetuses in early pregnancy. It has been reported that during this period the BPD of male fetuses is 0.8 to 1.1 mm larger than that of female fetuses, and that BPD grows by 0.44 mm per day [Persson *et al.*, 1978]. Measurements of < 1 mm are within the error margin of the ultrasound technique and measurements of fractions of millimeters are currently not used in practice.

Some authors claim that fetal gender is one of many factors (including, parity and maternal age) influencing the accuracy of dating, but the differences are very small and of no clinical importance [Henriksen *et al.*, 1995; Tunón *et al.*, 1998]. In an investigation comprising 571617 women, Källén [2002] concluded that male fetuses are more likely than female ones to be judged older than the LMP date suggested at early fetometry. The estimated magnitude of the systematic error of gender difference corresponded to 1.5 days. Similar findings have been reported by Tunón *et al.* [1998], who calculated the difference in EDD between the genders to be 1.6 days; but, with females having a longer gestation. Other authors have calculated the gender difference to be up to 2.5 days [Moore *et al.*, 1988; Kieler *et al.*, 1995].

### ***Impact of ethnicity***

Some studies have shown the pregnancy duration to be 2-8 days longer in the white race than in the black [Hendersson & Kay, 1967; Papiernik *et al.*, 1990], but Collins *et al.* [2001] concluded that African Americans and Mexican Americans have higher postterm delivery rates than Whites. Ethnic group is only one of many demographic variables affecting the fetal size and growth pattern - others include parity and maternal height and weight, and fetal gender [Altman & Coles, 1980; Gardosi *et al.*, 1992].

## **CHARACTERISTICS OF POSTTERM PREGNANCY**

### ***The postterm placenta***

The classical explanation of the increased risk of perinatal mortality and morbidity in the postterm period is a gradual impairment of placental function after term [Cunningham *et al.*, 1997]. Signs of placental aging are observed as early as from the fifth month of gestation, at a time when the placenta is fully developed [Vorherr, 1975]. The aging process is compensated by a fivefold increase in the number of trophoblastic villi and an increase in the surface area of the vasculosyncytial membranes, in order to maintain an adequate fetal oxygenation and nutrient supply. The placental maturation and function reach a peak at 36 weeks of gestation. However, the morphological degeneration is not accompanied



by a functional decrement, although a gradual decline in placental transport with a reduction of placental and fetal growth is common near term.

The consequence of an aging placenta is believed to be a postmature fetus, which in the older literature was reported to occur in 20 to 40 % of postterm pregnancies [Vorherr, 1975; Schneider *et al.*, 1978].

## ***The amniotic fluid***

### **Amniotic fluid volume and amniotic fluid index**

During the first 20 weeks of gestation the amniotic fluid is produced by passive transport of water across the fetal skin, until keratinization occurs at 17-20 weeks [Brace, 1989]. After 20 weeks, the amniotic fluid is maintained entirely by the balance between the fetal urine production and fetal swallowing and by resorption across the amniotic and chorionic membranes to the fetal and maternal circulations [Peipert *et al.*, 1991]. The amniotic fluid volume increases steadily from approximately 200 mL at 16 weeks of gestation to 980 mL at 34 to 35 weeks, whereafter it decreases to approximately 800 mL at 40 weeks and 540 mL at 42 weeks [Queenan *et al.*, 1972; Brace, 1989]. A progressive reduction of the fluid volume by 150 mL/week occurs between gestational weeks 38 and 43 [Elliott & Inman, 1961]. Decreases in amniotic fluid volume can occur quickly during the postterm period [Clement *et al.*, 1987], when, as in other instances of oligohydramnios, associated with decreased fetal movements [Ahn *et al.*, 1987].

The amniotic fluid volume can be estimated semiquantitatively by ultrasound measurements. The first ultrasound method to be introduced comprised measurement of only the largest vertical pocket of fluid, and the lower limit for oligohydramnios was set to less than 1 cm when the fluid was measured in two planes perpendicular to each other [Chamberlain, 1984]. However, several investigators questioned the diagnostic accuracy of this method, and Phelan and colleagues [1987] therefore developed the amniotic fluid index (AFI) as a sum of vertical measurements of the largest amniotic fluid pocket in each of four quadrants, dividing the uterus into upper and lower segments and with the linea nigra indicating the right and left halves. The measured pockets should not contain the umbilical cord. Oligohydramnios is then defined as an AFI of less than 5.0 cm at term, and polyhydramnios as an AFI of 20 cm or greater.

### **Oligohydramnios**

In 1975, Vorherr suggested that oligohydramnios in the postterm period may be caused by a compensatory redistribution of fetal blood flow, resulting in renal hypoperfusion concomitant with maintenance of an adequate blood flow to the fetal brain [Vorherr, 1975]. Oligohydramnios commonly develops as pregnancy advances past 42 weeks. A decreased amniotic fluid volume is associated with a risk of cord compression and abnormal fetal heart rate patterns [Gabbe *et al.*, 1976; Rutherford *et al.*, 1987]. After rupture of the membranes, amnioinfusion might prevent these problems [Miyazaki & Taylor, 1983]. Many investigators have reported an increased risk of cesarean section (CS) for fetal distress in postterm pregnancy with oligohydramnios and also an association with meconium stained fluid [Crowley, 1980; Phelan *et al.*, 1985].

Oligohydramnios is also a prevalent component in preeclampsia with maternal vasoconstriction and a secondary reduction of the uteroplacental blood flow [Goodlin *et al.*, 1983], as well as in situations with maternal hypovolemia [Sherer *et al.*, 1990] and in fetuses suffering from growth restriction [Gohari *et al.*, 1977; Manning *et al.*, 1981].

### **Meconium stained amniotic fluid and meconium aspiration syndrome**

Meconium stained amniotic fluid is a result of passage of fetal colonic contents into the amniotic cavity. The overall incidence is approximately 12 %, but a figure as high as 30-40 % can be reached in postterm pregnancy [Miller & Read, 1981; Ahanya *et al.*, 2005]. The underlying mechanisms are still not completely understood and are debatable, with a number of different theories. Saling [1968] proposed that passage of meconium is due to mesenteric vasoconstriction, causing hyperperistalsis and anal sphincter relaxation. Walker [1959] observed passage of meconium when the umbilical venous oxygen saturation decreased to below 30 %. Other theories are that vagal stimulation secondary to cord compression can cause passage of meconium [Hon, 1963], and that presence of meconium in the amniotic fluid is a normal physiological phenomenon even in fetuses without distress.

Several authors have reported an association between chorioamnionitis and meconium stained amniotic fluid [Romero *et al.*, 1991; Usta *et al.*, 1995], and in the presence of both conditions meconium aspiration syndrome (MAS) commonly

occurs. MAS is accompanied by an increased incidence of low Apgar scores [Krebs *et al.*, 1980; Starks, 1980; Steer *et al.*, 1989] and high morbidity and mortality [Fenton *et al.*, 1962; Hobel, 1971; Krebs *et al.*, 1980], although not all studies have confirmed these relationships [Meis *et al.*, 1982; Mitchell *et al.*, 1985]. Thus, the presence of meconium stained fluid in an otherwise normal labor without fetal heart rate abnormalities and independent of gestational age, does not indicate a risk for an adverse fetal outcome and can be managed with close monitoring alone [Bochner *et al.*, 1987; Baker *et al.*, 1992].

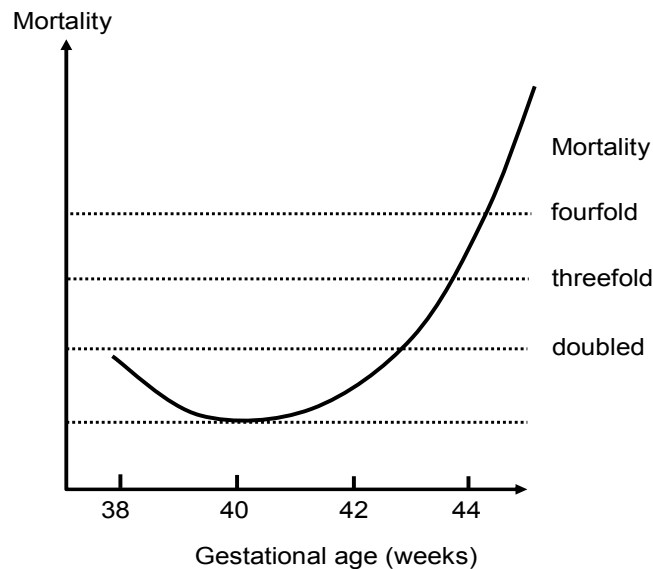
### ***Fetal macrosomia***

Large fetuses may be constitutionally large or they may be large as a consequence of a pathological process, such as maternal diabetes mellitus or obesity, or because of continued growth in postterm pregnancy. Fetal macrosomia is not equivalent to growth acceleration or large-for-gestational-age (LGA), but occurs when a fetus has grown above a certain limit. There is no consensus on the definition of fetal macrosomia in the literature: some regard a fetal weight above 4000 g as macrosomia, others above 4500 g or 5000 g.

Even with sonographic measurements an accurate diagnosis of macrosomia can be difficult. The error range has been estimated to be up to 15 % ( $\pm 2$  SD) and the information about estimated weight is therefore of limited clinical value [Gonen *et al.*, 1997]. The importance of recognizing macrosomia lies in the complications associated with this condition. These include increased maternal and fetal trauma, shoulder dystocia with resulting Erb's palsy, perinatal ashyxia, meconium aspiration, and postpartum hemorrhage [Chervenak *et al.*, 1989].

### ***Fetal and neonatal risks***

The perinatal mortality rate displays a U-shaped curve with its nadir at 40 weeks [Campbell *et al.*, 1997; Ingemarsson & Källén, 1997; Divon *et al.*, 1998] (Fig.1).



**Figure 1.** Perinatal mortality related to gestational age.

In older studies, with insufficient dating and restrictive use of induction of labor (IOL), the increase in mortality postdate was more steep than it is nowadays [Evans *et al.*, 1963]. The higher mortality is mainly due to intrauterine growth restriction (IUGR), suggesting that much effort should be made to identify such fetuses at an earlier gestational age. In uncomplicated cases with adequate fetal surveillance, the mortality figures in postterm pregnancy are almost equal to those in term pregnancy [Dyson, 1988], but in the presence of fetal growth restriction the figures are five times higher in postdate than in term pregnancy [Campbell *et al.*, 1997; Divon *et al.*, 1998]. In a Swedish 10-year material from 1982 to 1991, the fetal death rate for nulliparae was 2.72/1000 at 38 weeks, 1.23/1000 at 40 weeks, and in the postterm period 2.26/1000 [Ingemarsson & Källén, 1997]. No differences were found for multiparae. The mortality figures are also correlated to smoking, fetal growth restriction, and maternal age over 35 years [Raymond *et al.*, 1994]. In comparison with term pregnancy, the dominating causes of fetal death in postterm pregnancy are intrapartum asphyxia and aspiration of meconium [Hovi *et al.*, 2006].

Not only the mortality but also the morbidity is increased in postterm pregnancy [Divon *et al.*, 1998]. The perinatal morbidity panorama includes fetal distress, mainly explained by cord compression, neonatal seizures, meconium aspiration, pneumonia, and shoulder dystocia [Leveno *et al.*, 1984; Sachs & Friedman, 1986; Eden *et al.*, 1987b]. In uncomplicated postdate pregnancy, the fetus gains weight continuously, increasing the risk of macrosomia with difficult labor and traumatic injuries such as cephalhematoma, fractures, and brachial plexus injury [Eden *et al.*, 1987b; Campbell *et al.*, 1997].

### **Fetal acid-base balance**

Acidosis is a condition with an accumulation of hydrogen ions ( $H^+$ ) in the blood and can be classified into three basic types: metabolic, respiratory, and mixed. The type is based on the blood levels of bicarbonate ( $HCO_3^-$ ) and  $pCO_2$ . Uncompensated metabolic acidosis is characterized by a normal  $pCO_2$  and decreased  $HCO_3^-$ , respiratory acidosis by an increased  $pCO_2$  and normal  $HCO_3^-$ , and mixed acidosis by an increased  $pCO_2$  and decreased  $HCO_3^-$ .

In 1909, the Danish chemist Søren Sørensen described the influence of the hydrogen ion concentration on biochemical reactions. He proposed the exponential scheme for representing the hydrogen ion concentration as  $pH = 10^{-C_H} = -\log^{C_H}$ , i.e., the negative logarithm of the  $H^+$  concentration. p, the first letter in 'power', was called the  $H^+$  exponent and the expression was later changed to pH. The relationship with carbon dioxide and bicarbonate is illustrated by the Henderson-Hasselbalch equations summarized below, where pK is the negative logarithm of the dissociation constant:

$$pH = pK + \log (\text{base} / \text{acid})$$

$$pH = pK + \log (HCO_3^- / H_2CO_3)$$

There is no consensus on the pH definition of fetal acidosis at birth. In Sweden, a cord artery pH of less than 7.10 is traditionally considered indicative of fetal acidosis. This value corresponds to the mean value minus two standard deviations (SD) [Helwig *et al.*, 1996; Herbst *et al.*, 1997]. Other authors have used an index value of 7.20 [Bretscher & Saling, 1967], whereas a cutoff at 7.00 seems to represent a critical limit for the risk of neonatal death or neurological sequelae [Gilstrap *et al.*, 1989; Goldaber *et al.*, 1991].

### ***Maternal risks***

It is well known that postterm pregnancy carries an increased risk of maternal complications. The risks are mainly related to obstetric interventions such as induction of labor with a subsequent prolonged course of labor and risk of operative delivery. Management of uterine inertia often leads to obstetric trauma due to operative delivery with forceps, ventouse or CS [Campbell *et al.*, 1997]. Prolonged labor as well as operative delivery also increases the risk of excessive maternal bleeding [Bergholt *et al.*, 2003] and intrauterine infection.

## **FETAL SURVEILLANCE PROGRAM**

No tailor-made fetal surveillance methods are explicit for the postterm period, and traditional methods are therefore used.

### ***Fetal cardiotocography***

Bartnicki and colleagues [1992] reported that the fetal heart rate (FHR) pattern in postterm pregnancy is different from the pattern at term. A significant decrease in the number of accelerations, decreased variation, a shorter duration of high variation episodes and a lower baseline were noted in postterm pregnancies, findings which should be taken into account in the interpretation of the postterm pregnancy cardiotocogram.

### **Nonstress test**

The nonstress test (NST) is widely used in postterm pregnancy and it is recommended that it is performed 2-3 times weekly or every second day [Arulkumaran, 1989]. A reactive test signifies fetal wellbeing when two or more accelerations of 15 beats/min or more occur, each lasting for 15 s or longer. Fetal heart rate decelerations at an NST are predictive of increased fetal and neonatal morbidity and an increased risk of fetal and neonatal death in postterm pregnancy [Benedetti & Easterling, 1988]. Such decelerations may be due to cord compression secondary to oligohydramnios. Many authors recommend induction of labor in cases of oligohydramnios, regardless of whether the NST is normal or not [Small *et al.*, 1987; Divon *et al.*, 1995]. However, the ability of NST, when

used alone, to preclude an acute asphyxial insult or predict a poor perinatal outcome is low. Miyazaki *et al.* [1981] reported a poor outcome in 8 % of cases with a normal NST, giving a false reassurance of fetal wellbeing.

### **Contraction stress test**

The contraction stress test (CST), often performed as an oxytocin challenge test (OCT), has the advantage that any negative result appears to predict fetal wellbeing for at least 7 days [Cooper *et al.*, 1975]. Major disadvantages of the CST/OCT are that it is cumbersome to perform and that the frequency of equivocal tests is reportedly as high as 35 % in postterm pregnancies [Lagrew, 1995]. Prompt delivery with CS is almost invariably required after a nonreactive positive test [Freeman *et al.*, 1976].

### **Ultrasound examination**

The purposes of ultrasound examinations in postterm pregnancy are mainly to detect oligohydramnios, fetal growth restriction, and macrosomia. A decreasing amniotic fluid volume from 36 weeks of gestation towards term and beyond is a normal phenomenon [Montan & Malcus, 1995]. A pronounced reduction of the amniotic fluid volume can occur rapidly and the fluid can even disappear within 24-48 hours. Measurements of AFI therefore need to be performed every second or third day. When AFI is > 50 mm, conservative management is common practice. To identify postterm fetuses that are at greatest risk, presence of oligohydramnios can be used alone [Crowley *et al.*, 1984] or in conjunction with a fetal biophysical profile [Phelan *et al.*, 1984].

A second ultrasound scan at 32-33 weeks for estimation of fetal growth is routine at the Malmö University Hospital. Detection of IUGR antenatally has a decisive influence on the perinatal outcome, as recently shown by Lindqvist & Molin [2005]. Single symphysis-fundus measurements in the period following the routine scan have a very limited value, and can only occasionally raise a suspicion of IUGR. Since a majority of third trimester IUGR cases are detected at the second routine scan, few cases may remain to the postterm period.

### **Doppler ultrasound velocimetry**

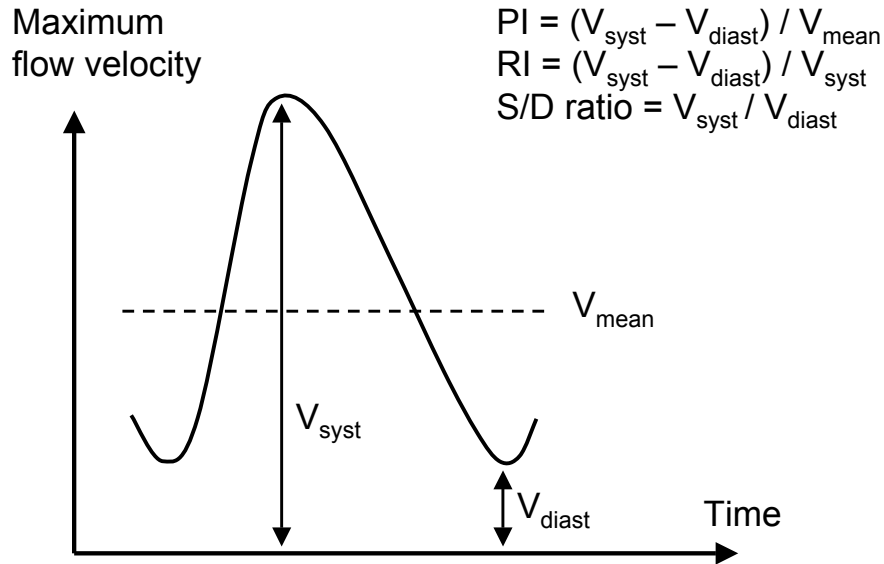
Christian Johann Doppler described the Doppler phenomenon in 1842, and the use of Doppler ultrasound in fetal surveillance was introduced in the 1970s [Fitzgerald & Drumm, 1977; McCallum, 1977].

The Doppler principle is based on changes in the frequency of wave energy when the energy is reflected by a moving object; the frequency shift being proportional to the velocity of the reflector. Different Doppler ultrasound techniques are used in obstetrics, namely continuous wave (CW) Doppler, pulsed wave (PW) Doppler, color Doppler imaging (CDI), and power Doppler (PD). Only PW Doppler ultrasound will be discussed here. PW Doppler transmits short pulse sequences of ultrasound, where echoes from a moving object (blood cells) are received after a short interval of time, allowing measurements of blood flow velocity. After identification of the vascular anatomy with CDI, the PW technique allows assessment of flow in a defined site of a defined vessel by placing the sampling volume at the site of interest.

Doppler velocimetry can be carried out in practically all vessels that can be identified with CDI. Numerous Doppler studies have been carried out by measuring blood flow in such vessels as the maternal uterine arteries, umbilical vessels, fetal aorta, renal arteries, and cerebral arteries and veins. Since volume flow measurements are unreliable with the Doppler technique, measurements of the maximum flow velocity waveform (FVW) and calculation of different indices reflecting peripheral vascular flow resistance are universally used. The FVW profiles vary considerably between different vessels.

In the early era of obstetric Doppler velocimetry, FVWs were measured in the fetal descending aorta and the umbilical vein [Gill & Kossoff, 1979; Eik-Nes *et al.*, 1984]. Lingman & Maršál [1986] presented normal reference values during the third trimester. The peripheral vascular resistance to blood flow is described with different indices, such as the resistance index (RI) [Planiol & Pourcelot, 1974], the systolic-diastolic ratio (S/D) ratio [Stuart *et al.*, 1980], and the pulsatility index (PI) [Gosling *et al.*, 1971] (Fig. 2). The PI has the advantage that it is more versatile when the diastolic flow falls to zero. When the diastolic flow is zero, the S/D ratio is infinity and  $RI = 1$ .





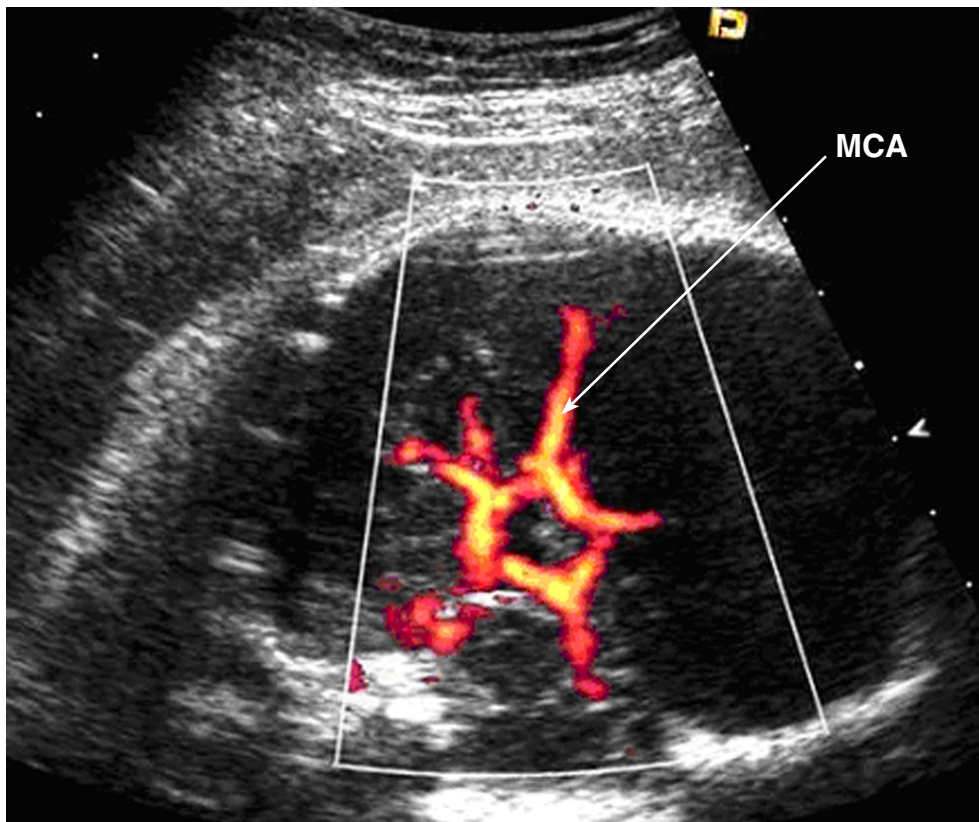
**Figur 2.** Flow velocity waveform analysis.  $V_{\text{syst}}$  denotes peak systolic velocity;  $V_{\text{diast}}$  = minimum diastolic velocity;  $V_{\text{mean}}$  = mean velocity over the heart cycle; PI = pulsatility index; RI = resistance index; S/D ratio = systolic/diastolic ratio.

To support the interpretation of blood flow measurements, semiquantitative classification systems have been introduced. The Blood Flow Class (BFC) system is used for the umbilical artery (UA) and the fetal aorta [Laurin *et al.*, 1987; Gudmundsson & Maršál, 1988], the uterine artery score (UAS) system for the uterine arteries [Sekizuka *et al.*, 1997; Gudmundsson *et al.*, 2003], and the placental score system for the uterine and umbilical arteries in combination [Gudmundsson *et al.*, 2003]. The BFC system is widely used in daily clinical management and is a good predictor of fetal compromise when this is expressed as operative delivery due to fetal distress and IUGR [Laurin *et al.*, 1987; Gudmundsson & Marsál, 1991].

**Doppler velocimetry in the cerebral circulation**

***Anatomy of the cerebral arterial circulation***

The anterior, middle, and posterior cerebral arteries supply the cerebral hemispheres. The fetal middle cerebral artery (MCA) measures 2-4 cm and is the largest branch of the circle of Willis, running laterally in the Sylvian fissure as a direct continuation of the internal carotid artery. MCA supplies most of the convexity of the cerebral cortex on each side of the hemispheres and the deep parts of the cerebrum, such as the basal ganglia and the internal capsule (Fig. 3)



**Figure 3.** Circle of Willis with middle cerebral artery (MCA)

***Cerebral fetal circulation and redistribution of blood flow***

The cerebral blood flow (CBF) can be quantified as volume blood flow in milliliters per 100 g brain tissue weight per minute (mL/100 g/min). The CBF adapts to changes in the uteroplacental and umbilicoplacental circulations to maintain the cerebral oxygen supply, and is mainly regulated by changes in pO<sub>2</sub> and pCO<sub>2</sub> [Lucas *et al.*, 1966; Jones *et al.*, 1977]. In situations of fetal hypoxia, blood flow is redistributed to vital organs such as the heart, brain, and adrenal glands [Dubiel *et al.*, 1997; Jensen *et al.*, 1999], and the CBF increases to protect the brain from hypoxic injury [Friss-Hansen, 1985; Vyas *et al.*, 1990]. In the cerebral arteries, this redistribution of blood flow can be recorded as a decreased vascular resistance in the fetal MCA [Arbielle *et al.*, 1987] and anterior cerebral artery [van den Wijngaard *et al.*, 1989; Noordam *et al.*, 1994]. This “brain-sparing” phenomenon is prevalent in growth-restricted fetuses [Marsál *et al.*, 1984; Arduini *et al.*, 1987]. In addition to development of a brain-sparing flow (BSF), other regulatory systems for protecting the brain from hypoxic injury are activated, such as an increased extraction of oxygen from erythrocytes in peripheral tissues [Spencer *et al.*, 2000; Blackwell *et al.*, 2004], metabolic downregulation [Hunter *et al.*, 2003], and mobilization of glucose from glycogen stores [Asano *et al.*, 1994].

***Flow velocity in the middle cerebral artery***

The first FVW recordings reflecting the fetal cerebral circulation were obtained from the common carotid artery [Marsál *et al.*, 1984], the internal carotid artery, and MCA [Wladimiroff *et al.*, 1986]. Doppler measurements of MCA flow velocities can be carried out in the proximal, middle or distal part of the vessel. Flow in the latter segment is more influenced by behavioral states [Locci *et al.*, 1992] and is therefore more poorly reproducible. The PI tends to be lower in the proximal part than in the two distal parts [Locci *et al.*, 1992; Hsieh *et al.*, 2001]. The clinical importance of different sample sites was addressed by Figueras and colleagues [2004], who concluded that the proximal site MCA PI significantly predicts UA pO<sub>2</sub> but not pH at delivery, whereas the distal site MCA PI has a weak association with pH. Other observations have confirmed the correlation between proximal MCA PI and hypoxia during labor [Kassanos *et al.*, 2003].

Studies on MCA velocimetry in the postterm population have shown a continuous decrease in vascular flow resistance at the end of pregnancy [Kirkinen *et al.*, 1987;

Woo *et al.*, 1987; Brar *et al.*, 1988; Årström *et al.*, 1989; Locci *et al.*, 1992; Mari & Deter, 1992; Hsieh *et al.*, 2001]. This might be explained by a physiological change associated with an increase in cerebral metabolic requirements [Dobbing & Sands, 1970; Mari & Deter, 1992], or be secondary to a mild placental insufficiency with fetal hypoxemia, which may occur at this stage of gestation. However, other studies have not verified any decrease in MCA PI [Battaglia *et al.*, 1991] and suggest that the brain-sparing effect occurs only in situations with acute or chronic hypoxia. Devine and colleagues [1994] demonstrated that a low MCA-to-UA resistance ratio, also called the cerebroplacental ratio (CPR), is associated with an increased risk of fetal distress.

### **Biophysical profile**

The biophysical profile (BPP) was presented for the first time by Manning *et al.* [1980] and subsequently modified by Vintzileos *et al.* [1983], with the addition of placental grading. The BPP contains five different fetal variables: fetal breathing, fetal movements, fetal tone, amniotic fluid volume, and the nonstress test. Each normal variable is assigned a score of 2 when normal and a score of 0 when abnormal, with a maximum possible BPP score of 10. Neilson & Alfirevic [2000] made a meta-analysis of four randomized controlled trials to assess the effects of biophysical profile tests on the pregnancy outcome in high-risk pregnancies, and concluded that BPP did not differ from the others as a test of fetal wellbeing.

### **Fetal movements**

The fetal body movements are reduced with advancing gestational age as a result of an increase in fetal weight and a decrease in amniotic fluid volume. The presence of at least three discrete episodes of fetal movements during 30 minutes is considered as normal [Manning *et al.*, 1980; Vintzileos & Knuppel, 1994]. Observations of fetal body movements as a single method for fetal surveillance are insufficient, but studies have shown a negative correlation to fetal hypoxemia [Vintzileos *et al.*, 1991]. During development of fetal hypoxia, cessation of movements follows a predictable sequence: the fetal thoracic movements (breathing) disappear first, followed by movements of fetal extremities, and finally movements of the fetal trunk and spine; the latter parameter is then best correlated with fetal acidemia [Vintzileos & Knuppel, 1994].

## **MANAGEMENT OF THE POSTTERM PREGNANCY**

### ***Induction of labor***

The choice of method for induction of labor is strongly related to the cervical status, parity, reason for IOL, and length of gestation. In Sweden, the status of the cervix is usually described by Westin's modification of the Bishop score [Westin, 1977]. This describes the maturation of the cervix in a score from 0 to 10, where consistence, degree of effacement (length), extent of dilatation, position of the cervix, and the station of the presenting part each gives 0 to 2 points each. A score of 5 or more in multiparae and 6 or more in nulliparae is considered as favorable. The maturation of the cervix can be accelerated by application of either an intracervical jelly or intravaginal tablets or jelly containing prostaglandin E<sub>2</sub>. Other methods are oral prostaglandins (misoprostol), intracervical balloon placement, or simply artificial rupture of the membranes (amniotomy). In cases of a ripe cervix the method of choice for IOL is intravenous oxytocin infusion and amniotomy.

### ***Labor induction versus expectant management***

There are in principle two approaches in the management of postterm pregnancy: elective termination of pregnancy or expectant management with repeated fetal monitoring and selective IOL in cases with an anticipated complication. With the first approach, labor is induced electively when the pregnancy reaches 41-42 weeks of gestation. With the latter approach, the pregnancy is monitored closely with serial antenatal assessments of fetal wellbeing, and spontaneous labor is anticipated as long as there are no fetal or maternal problems. If complications develop, labor is induced or CS performed.

In general, labor induction is indicated when the benefits of delivery exceed the risks of continuing the pregnancy. There is a lack of scientific evidence on the optimal management of high-risk pregnancies continuing postdate, but elective delivery is the choice whenever significant maternal risk factors, such as hypertension and diabetes mellitus, occur in postdate pregnancies [Eden *et al.*, 1988]. In high-risk pregnancies the management options are often obvious, but in low-risk pregnancies approaching postterm the optimal time for delivery is controversial [Sanchez-Ramos *et al.*, 2003].

A Cochrane meta-analysis [Gülmezoglu *et al.*, 2006], including 19 controlled trials with almost 8000 participants, showed that routine induction in gestational week 41 or later was associated with fewer perinatal deaths compared with waiting for spontaneous labor for at least one week (1/2986 vs. 9/2953). However, the absolute risk was extremely small, i.e., 3/1000.

Several reports indicate that IOL increases the risk of cesarean delivery [Yeast & Jones, 1999; Maslow & Sweeny, 2000; Hovi *et al.*, 2006], although the Cochrane analysis [2006] did not provide such evidence. Risk factors associated with IOL and with CS are nulliparity, an unfavorable cervical status [Macer *et al.*, 1992; Seyb *et al.*, 1999; Maslow & Sweeny, 2000], and epidural analgesia [Macer *et al.*, 1992; Prysak & Castronova, 1998]. However, results from different studies are difficult to compare, on account of inclusion of heterogeneous groups of women, multiple indications, and use of different methods for induction. Alexander and colleagues [2001] investigated the effects of labor induction in a homogeneous cohort of prolonged low-risk women with a uniform induction and management protocol. They found that it was the above mentioned factors (i.e., nulliparity, an unripe cervix, epidural analgesia), and not the induction of labor *per se* that increased the risk of cesarean delivery.

Only a minority of women with postdate pregnancy have a cervix favorable for IOL. Harris and co-workers [1983] reported that only 8.2 % of women at 42 weeks had a ripe cervix. On the other hand, when a conservative attitude is exercised, approximately 50 % of the postterm women are expected to deliver spontaneously within 3 days [Ingemarsson & Hedén, 1989; Malcus *et al.*, 1991], even in gestations after 43 weeks [Olofsson & Saldeen, 1996]. This figure is also valid in uncomplicated twin pregnancies beyond term, where less than half of the group will remain after 4 days of conservative management [Kitlinski & Olofsson, 2007].

*Introduction*

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## **AIMS OF THE STUDIES**

The aims of the studies were:

to elucidate the question whether a fetal gender-dependent systematic 1.5-day dating error at ultrasound fetometry could lead to consequences such as unnecessary or late obstetric intervention in postterm pregnancy (*Study I*);

to find out whether commencement of intensified fetal monitoring in postdate pregnancies 1-3 days earlier than the postterm period could improve the obstetric and neonatal outcome and lower the morbidity and mortality in childhood (*Study II*);

to assess the clinical value of adding middle cerebral artery Doppler flow velocimetry to an already vigilant postterm surveillance program (*Study III*);

to define the reference intervals of pH in arterial cord blood as a function of gestational age in alert newborns at term, and further to compare the association between Apgar score and pH with application of a stationary definition of cord acidemia and of a gestational age-adjusted definition of low pH (*Study IV*).





## MATERIAL AND METHODS

### DEFINITIONS

The definitions of preterm, term, and postterm pregnancy used in this thesis do not refer to how and when a pregnancy is dated, but refer to a normal gestational length of 280 days (40 weeks) when calculated from the first day in the last menstrual period. In Sweden gestational age is described as *completed* weeks and days of pregnancy. This means that the expected day of delivery corresponds to 39 completed weeks and 6 completed days, written as 39+6 weeks. Expressions like ‘the 40<sup>th</sup> week’ (= 39+ weeks) should be avoided, both by professionals and the public, to avoid misunderstanding.

The following definitions were applied in the present studies:

**Preterm** pregnancy was defined as a pregnancy with a gestational length of less than 37 completed weeks (258 days,  $\leq 36+6$  weeks) [WHO, 1977; FIGO, 1986].

**Term** pregnancy was defined as a pregnancy with a gestational length from 37 completed weeks up to less than 42 completed weeks (259–293 days, 37+0 to 41+6 weeks) [WHO, 1977; FIGO, 1986].

**Postdate pregnancy** was defined as a pregnancy that had passed 40 completed weeks (280 days, 40+0 weeks) [WHO, 1977; FIGO, 1986].

**Postterm, or prolonged pregnancy** was defined as a pregnancy with a gestational length of 42 completed weeks (294 days, 42+0 weeks) or more [WHO, 1977; FIGO, 1986].

**Postmature** is not synonymous with prolonged pregnancy, although this terminology was used in the older literature. Dysmature is a word synonymous with postmature and is more preferable, since it does not refer to gestational age. Postmaturity, or dysmaturity, is a pediatric clinical term describing a newborn that has a scaphoid abdomen with minimal fat, dry peeling skin, overgrown nails, well-developed creases on the palms and soles, abundance of scalp hair, little vernix and

lanugo hair, an attentive apprehensive look, and is often coated with meconium [Clifford, 1954]. The umbilical cord, membranes and placenta are often meconium stained [Clifford, 1957; Sjöstedt *et al.*, 1958]. Dysmaturity is not pathognomonic for postterm pregnancy, but 20-40 % of all cases occur in postterm pregnancies.

**Oligohydramnios** was defined as an AFI < 50 mm when sonographically estimated with the four-quadrant method [Phelan *et al.*, 1987].

**Polyhydramnios** was defined as an AFI > 250 mm at ultrasound measurement.

**Preeclampsia** was defined as a blood pressure of  $\geq 140/90$  mmHg with albuminuria  $\geq 0.3$  g/L urine, recorded at least twice with an interval of at least 6 h.

**Intrauterine growth restriction (IUGR)** was defined as a sonographically estimated fetal weight below the gestational age-adjusted mean reference value [Maršál, 1996] minus 2 SD, corresponding to a weight deviation (WD) of  $-22$  % or more below the mean, or a decrease in WD of  $\geq 10$  % between two measurements.

**Appropriate-for-gestational-age (AGA)** was defined as a gestational age-adjusted birthweight within the mean  $\pm 2$  SD, **small-for-gestational-age (SGA)** as a birthweight below the mean minus 2 SD, and **large-for-gestational-age (LGA)** as a birthweight above the mean plus 2 SD.

**Neonatal distress** was defined as an umbilical cord artery blood pH of < 7.06 at postterm birth [Study IV], and/or an umbilical venous blood pH of < 7.15, and/or a 5- or 10-minute Apgar score < 7.

**Neonatal hypoglycemia** was defined as a plasma glucose concentration  $\leq 2.6$  mmol/L.

**Respiratory distress** in the neonate was defined as acute illness characterized clinically by a respiration rate  $\geq 60$ /min, dyspnea (intercostal, subcostal retractions, sternal retraction) with a predominantly diaphragmatic breathing pattern and a characteristic expiratory grunt or moan, all presenting within 4-6 hours of delivery.

## ETHICAL AND PUBLICATION APPROVALS

The use of register data was approved by the Medical Research Ethics Committee at Lund University. In addition, *Studies II* and *III* were approved by the Swedish National Board of Health and Welfare, Stockholm. Rules for publication of data from the Perinatal Revision South Register (PRSR), used in *Studies I* and *IV*, have been approved by the South Swedish Regional Board of Chairmen representing the involved departments. Informed consent from the participating women was not obtained, since they were part of a routine clinical management protocol without identification of individuals and the studies were retrospective.

## REGISTER DATA

Maternal, obstetric and neonatal demographic and maternal health care services data have been recorded systematically in Sweden for several decades. The purpose is mainly administrative, but for many years the data have also been recorded for research reasons. All individuals living in Sweden have a unique personal identification number (PIN). This consists of eight digits for the date of birth (year-month-day), followed by three digits to identify the individual, and a tenth digit, which is a check digit. The PIN can identify an individual in all national registers, since the system is used universally in Sweden.

### ***The local 'MacOB' database***

A local computerized obstetric and neonatal database (MacOB) was initiated at the Department of Obstetrics and Gynecology in Malmö in 1990. This database has gradually been developed and enlarged over the years. Midwives register all pregnant women at booking in the first trimester. Every outpatient clinic visit, antenatal admission, and delivery, and the neonatal outcome and the post-delivery follow-up are recorded by midwives, obstetricians and neonatologists. The database now contains more than 2000 different variables. MacOB is also a computerized obstetric medical chart and it is also possible to perform searches in the medical chart texts with specific words or sentences. In October 2006, the database contained information on about 75500 deliveries. The principal aims of

the MacOB are obstetric quality assurance, recording of vital statistics, and facilitation of research.

### ***The Perinatal Revision South Register***

The PRSR is a perinatal and neonatal quality assurance research project initiated by Professor Karel Maršál and it started in 1994. It comprises all maternity units in the southern Swedish region, with a population of approximately 1.6 million and with 17000 annual deliveries. After closure of two small maternity units, the original 11 hospitals are now 9. Two of the units are university clinics with 3500-4000 deliveries each per year, five are central hospitals with 1500-3100 deliveries, and two are county hospitals with about 1000 deliveries annually.

The aim of the PRSR is to provide a basis for regional obstetric and neonatal quality assurance. On a regular basis, consecutively collected perinatal data are reported to the central PRSR office at the university hospital in Lund [Molin, 1997].

### ***The Swedish Medical Birth Register***

The Swedish Medical Birth Register (SMBR) was established in 1973 by an Act of the Swedish Parliament. The purpose of the register is to compile information on ante- and perinatal factors, and their importance for the health of the infant. The PIN of a newborn is linked to the SMBR from The Birth Register at Statistics Sweden. The SMBR contains the basic record of antenatal care of the mother (including social factors and maternal history), the delivery record, and the record from the pediatric examination of the newborn infant. Only 1-2 % of the records are missing and the register is a valuable source of information for reproduction epidemiology.

### ***The Patient Register***

This register, formerly known as the In-Patient Register or Home-Discharge Register, started in 1964 and is administered by The Swedish National Board of Health and Welfare. The register has provided almost complete coverage of hospital discharges and diagnoses in Sweden since 1987. The Patient Register includes data such as age, sex, the unique personal identification number, when and

where the admission took place (hospital, clinic, department, etc.) and the reason for hospital treatment (ICD diagnosis codes, operation codes, etc.).

### ***The Cause of Death Register***

Swedish statistics on causes of deaths are among the oldest in the world. Recording of this information was introduced as early as in 1749 and the responsibility for reporting a death initially lay with the clergy. At the end of World War II, the World Health Organization (WHO) took over the responsibility for international coordination. Statistics on causes of death were published by Statistics Sweden on a yearly basis between 1911 and 1993. Since 1994, The Swedish National Board of Health and Welfare has been responsible for these statistics and publication. Complete data from 1961 onwards can be obtained, whereas earlier information is of less good quality.

## **MATERIAL**

*Study I* was a population-based, multi-center consecutive study. From the 6-year period of 1995-2000, data from 82484 singleton pregnancies at  $\geq 37$  completed gestational weeks with ultrasound dating were retrieved from the PRSR. Cases of fetal growth restriction, congenital malformations or chromosomal abnormalities were not identified in this study and were therefore not excluded from the material. The exclusion criteria were multiple pregnancy, accurate dating by ultrasound missing, and delivery by planned cesarean section.

*Study II* comprised a Malmö material ('MacOB') from 1990 to 2005. During this period, complete data on 2032 women with antenatally uncomplicated postdate/postterm singleton pregnancies were available. The initial maternal and fetal evaluation, which is scheduled to day 294 of pregnancy, was performed earlier when day 294 fell on a weekend or holiday, and therefore the results could be evaluated in a quasi-randomized controlled manner. Group A included 322 women with initial postterm controls on day 291 or 292, Group B included 334 women attending on day 293, and Group C with 1366 women attending on day 294 or 295. A search for morbidity was performed in the Patients Register and for mortality in the Cause of Death Register. A control group comprising 11784 antenatally uncomplicated singleton pregnancies delivered at 40+0 weeks  $\pm$  3 days

was also retrieved and served as controls for the evaluation of long-term morbidity and mortality.

In *Study III*, obstetric and neonatal data between 1992 and 1996 were obtained from the 'MacOB' register in 229 pregnant women with an uncomplicated singleton pregnancy attending their first out-patient postterm evaluation at 42 completed gestational weeks (294 days, range 292-296 days due to weekends and holidays). The results of middle cerebral artery (MCA) Doppler flow velocimetry, performed in addition to the routine fetal surveillance program, were blinded for the managing obstetricians. Childhood morbidity necessitating hospital admission was retrieved from the Patients Register and information about mortality from the Cause of Death Register.

In *Study IV* data were collected from the PRSR. The study comprised a 6-year period from 1995 to 2000. Inclusion criteria were singleton pregnancies aimed for vaginal delivery after 37 completed gestational weeks and for which information on year of birth, delivery unit, maternal age and parity, and Apgar scores was available in the database. Exclusion criteria were elective cesarean delivery, preterm delivery, multiple pregnancy, and cases without pertinent information. With the aim to define cord artery pH reference intervals of alert term newborns, 24390 singleton newborns with an Apgar score of 9 or greater at 5 minutes were included (cohort 1). This cohort was retrieved only from the two university departments where cord blood analysis was routinely done in all newborns. At the other nine departments, cord blood gas samples were analysed at the discretion of the obstetric staff. With the aim to investigate potential risks associated with a low pH, cord blood gas status was available in 44978 (cohort 2) of 82386 cases (cohort 3) collected from all 11 hospitals.

## **METHODS**

### ***Ultrasound***

Dating of pregnancy has been offered routinely to all pregnant women in Malmö since 1972 and is performed by early second trimester ultrasound fetometry scheduled to take place at 17-19 weeks of gestation [Persson & Weldner, 1986]. A

second routine scan at 32-33 weeks for estimation of fetal growth was introduced in the early 1980s.

Specially trained midwives perform the routine scans. In cases of a suspected abnormality, the woman is referred to a highly qualified obstetrician for further targeted examination. A routine scan in the second trimester includes determination of fetal viability and of the number of fetuses, estimation of gestational age, detection of any serious malformations, and assessment of the placental lie.

### **Ultrasound dating**

Measurement of the gestational sac (GS) is uncertain, because of the often irregular shape of the sac, and dating by GS measurements is inadequate without confirming the existence of an embryo. With appearance of an embryo or fetus, the CRL can be measured. Dating from CRL has a methodological dispersion of  $\pm 2.3 - 2.6$  days (SD) [Selbing & Fjällbrant, 1984; Wisser *et al.*, 1994].

At the Malmö University Hospital, pregnancies are routinely dated by measurements of biparietal diameter (BPD) and femur length (FL). The BPD is measured from the outer to the inner contour of the skull as described by Campbell *et al.* [1968], and FL is measured by the method of O'Brien *et al.* [1981]. The accuracy of dating by BPD and FL before gestational weeks 20 is within  $\pm 3$  days (SD) and the total methodological variation is not greater than  $\pm 10$  days. Measurements after 26 weeks of gestation have a methodological variation of  $\pm 1 - 1.5$  weeks (SD).

The following are three practical formulas that can be used between weeks 13 and 27 to estimate gestational age [Persson & Weldner, 1986]:

$\text{BPD} \times 1.2 + \text{FL} + 49 = \text{gestational age in days}$

$\text{BPD} \times 2.1 + 39 = \text{gestational age in days}$

$\text{FL} \times 2.46 + 59 = \text{gestational age in days}$

### **Doppler ultrasound flow velocimetry**

Doppler examinations in *Studies II* and *III* were performed with an Acuson 128 XP (Acuson, Mountain View, CA, U.S.A) scanner equipped with a multihertz (3.5 or 5 MHz) pulsed Doppler probe with color Doppler options. The high-pass filter was



set at 125 Hz. The output energy of the Doppler instrument did not exceed 100 mW/cm<sup>2</sup> (spatial peak temporal average intensity).

All Doppler recordings were performed with the mother in a semi recumbent position tilted slightly to the left and during fetal quiet resting and apnea, as determined both by direct visual observation with real-time ultrasound and by the absence of Doppler flow velocity waveform patterns typical of fetal gross movement and breathing. Specially trained expert ultrasound technicians carried out all examinations.

### ***Umbilical artery blood flow measurements***

The umbilical artery FVWs were recorded from a free-floating part of the cord. The mean umbilical artery pulsatility index (UA PI) was calculated from 10 consecutive heart cycles with Doppler recordings of optimal quality, and classified according to reference values [Gudmundsson & Maršál, 1988]. With reference to the PI value and end-diastolic flow (present, absent, reversed), the FVWs were classified according to a semi quantitative BFC system [Laurin *et al.*, 1987; Gudmundsson *et al.*, 2003].

### ***Middle cerebral artery blood flow measurements***

The MCA was identified by color Doppler ultrasound as a major lateral branch of the circle of Willis running anterolaterally toward the lateral edge of the orbit on a transverse section of the fetal head at the level of the cerebral peduncles. Pulsations in the MCA in the Sylvian fissure were identified. The pulse Doppler gate was applied to the middle portion of the vessel and FVWs were recorded at an insonation angle within  $\pm 15^\circ$ . Minimal pressure on the mother's abdomen was applied to avoid fetal head compression by the transducer.

The MCA PI in postterm pregnancy was classified as normal when it was between the 5th and 95th centiles according to gestational age-adjusted reference values [Palacio *et al.*, 2004]. The normal range of MCA PI at a gestational age of 294 days will then be 0.80 to 1.74. An MCA PI < 0.80 is below the 5th percentile and indicates brain-sparing flow. The CPR was defined as the MCA PI divided by the UA PI, where a CPR value of < 0.82 indicated BSF [Palacio *et al.*, 2004].

### ***Umbilical cord blood gases***

Umbilical cord blood acid-base analysis provides an objective method for evaluating the condition of a newborn with regard to hypoxia and acidemia. Of the hospitals in the South Swedish Health Care Region, cord blood gas analyses were routinely performed at the university hospitals in Malmö and Lund, and at the other hospitals at the discretion of the obstetric staff.

The cord was double clamped immediately after delivery and ideally before the newborn's first breath, as a delay as short as 20 seconds can significantly alter the arterial pH and pCO<sub>2</sub> [Lievaart & de Jong., 1984]. An artery and the vein were punctured separately and approximately 2 mL of blood was drawn into a plastic syringe previously flushed with a heparin solution (1000 U/mL). The samples were analyzed within 15 minutes. The analyses included pH and base excess. Blood gas determinations in Malmö and Lund were performed with blood gas analyzers ABL 500<sup>TM</sup> (Radiometer Medical A/S, Copenhagen, Denmark), measuring pH and pCO<sub>2</sub> by ion-sensitive glass electrodes.



## **STATISTICAL METHODS**

Values for variables are presented as mean  $\pm$  SD. SD is a measure of the variability of individual values around the sample mean, and mean  $\pm$  2 SD will contain approximately 95 % of normally distributed observations in an unselected population.

The Chi-square ( $\chi^2$ ) test evaluates the statistical significance of differences between proportions of two or more groups in a data set. When two or more groups are compared, the data are often presented in the form of a frequency table, also called a contingency table. If the degree of freedom is  $> 1$ , the sample size should be reasonably large when applying the Chi-square test, i.e., 80 % of the cells in the table should have expected frequencies greater than 5, and all cells should have expected frequencies greater than 1.

Fisher's exact test is used to examine the significance of the association between two variables in a 2x2 contingency table, when the cell sample size is  $< 5$ . For Fisher's exact test there is no sample size restriction.

Simple linear regression analysis was used to describe a relationship between two variables on the numerical scales. Simple linear regression analysis refers to the fact that correlation and regression measure only a linear relationship between two variables

The Mann-Whitney  $U$  test, also called the Wilcoxon rank-sum test or Mann-Whitney-Wilcoxon rank-sum test, is a nonparametric test that is used for comparison of means and distributions of two independent groups when the data do not meet the normal distribution requirements for a  $t$ -test. It is an excellent alternative to the  $t$ -test, as it is almost as powerful as the  $t$ -test in detecting a true difference when the observations follow a normal distribution.

The Z-test was used to compare the difference between a sample mean and the population mean. The SD in the two groups must be known and the sample material distributed normally. Generally, the sample size should be  $\geq 30$ .

Two-tailed tests were performed in all studies. A two-tailed test is appropriate when the researchers have no *a priori* expectation regarding the values they observe. With any significant deviation from the reference value, the null hypothesis is rejected. In contrast, a one-tailed test strategy is used when the researchers have directional expectations concerning the observed values.

A two-tailed  $P$  of less than 0.05 was regarded as statistically significant. Risk assessments were expressed as odds ratio (OR) according to the Mantel-Haenszel technique [1959]. To estimate the 95 % confidence interval (CI), Miettinen's method [1974] was used.

Correction for ties was applied when two or more identical values occurred in a sample of 'granulated' variables (continuous variables that have been converted into discrete variables by rounding off).

Logarithmic transformation of individual values in a sample is a way to handle a skewed distribution of values. A log transformation spreads out the smaller values and 'compresses' the larger values. By log transformation a skewed material may become normally distributed and parametric statistical tests can then be applied to log values.

Tests of homogeneity of the ORs across strata were based on weighted sums of the squared deviations of the stratum-specific log-ORs from their weighted means.

Stratification means that a population sample is first divided into relevant strata (subgroups) and that statistical comparisons are then made not only between samples but also separately in each stratum. In *Studies I* and *IV* stratifications were made for year of delivery, maternal age (5-year classes), and parity (previous deliveries 0, 1, 2, or 3 +) and additionally for delivery unit in *Study IV*. Other common strata in medicine are gender and severity and duration of a disease.

Type 2 error, also called the 'false negative' occurs when the observer is failing to observe a difference when in truth there is one. When small samples are used, the power is low, and the risk of accepting the null hypothesis when in fact it is false, is increased.

The statistical analyses were performed with the aid of StatView<sup>®</sup> (SAS Institute, Cary, NC, U.S.A) and MedCalc<sup>®</sup> (MedCalc Software, Mariakerke, Belgium) computer software, and also manually.



## RESULTS AND COMMENTS

### Skewed fetal gender distribution in prolonged pregnancy: a fallacy with consequences (**Study I**)

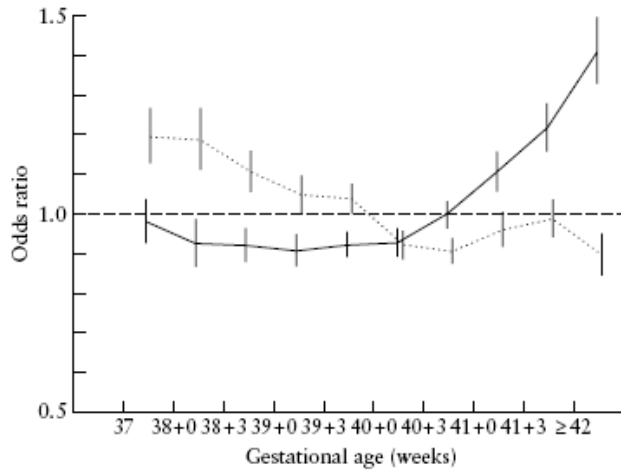
This study addressed the question whether a fetal gender-dependent systematic 1.5-day dating error at ultrasound fetometry in the early second trimester could lead to adverse consequences, such as unnecessary or unduly late obstetric intervention in postterm pregnancy.

#### **Results**

A strong positive association was found between male gender and a gestational age > 41 weeks as judged by ultrasound. At  $\geq 42$  weeks, the stratified odds ratio (OR) for male gender was 1.41 (95 % CI, 1.33-1.49). After adjustment of gestational age by  $\pm 0.75$  day (in practice, in 3 of 4 cases adjustments were made by  $\pm 1$  day), the stratified OR for distribution by male gender decreased to 0.90 (95 % CI = 0.84-0.95). Similar changes was noted in the boy:girl ratio at a gestational age of  $\geq 42$  weeks: before adjustment 2834:1965 = 1.44, after adjustment 2253:2406 = 0.94.

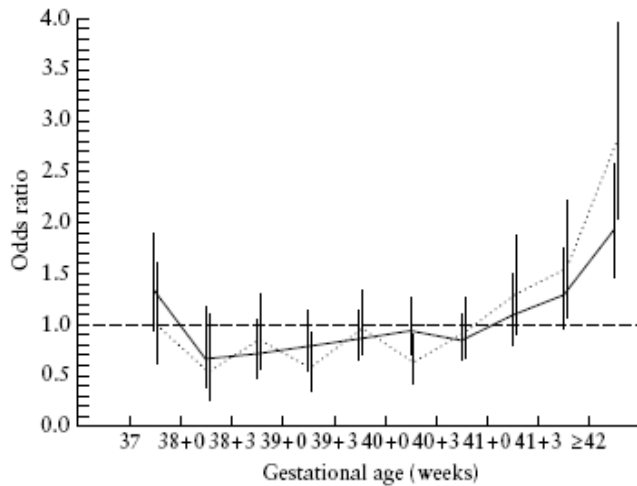
No gender difference in the rate of IOL was found in relation to the ultrasound-determined gestational age (OR = 1.07, 95 % CI = 0.95-1.20), either at term or postterm. The proportions of induced cases at a gender-adjusted gestational age of  $\geq 42$  weeks were 45 % and 28 % among male- and female-fetus pregnancies respectively. This implied an increased risk of male-fetus pregnancies being induced (IOL, male vs. female,  $P < 0.0001$ , OR = 2.11, 95 % CI = 1.87-2.38) (Fig. 4).





**Figure 4.** Male fetal gender as a risk factor for postterm delivery. Gestational age according to ultrasound (—) and adjusted for fetal gender (·····) are shown.

There was a significantly higher risk that postterm newborns, of both genders, would have an Apgar score of < 7 at 5 min, compared to term newborns. The magnitude of this association was higher among females than among males (OR = 1.9 for males and 2.8 for females), but the difference was not statistically significant ( $P$  for homogeneity = 0.087) (Fig. 5).



**Figure 5.** Postterm delivery as a risk factor for Apgar score < 7 at 5 min for males (—) and females (·····).

## Comments

*Study I* confirmed previously reported findings that with ultrasound dating in the early second trimester male gender fetuses are over-represented in postterm pregnancy. According to Källén [2002], the gender size difference at ultrasound fetometry in the second trimester corresponds to 1.5 gestational days, and by correction for this difference the increased chance of having a boy in a postterm pregnancy was reduced from an OR of 1.41 to 0.90. Tunón *et al.* [1998] calculated the difference in EDD between the genders to be 1.6 days, with females having a longer gestation. However, as shown in *Study I*, compared to female-fetus pregnancies male-fetus pregnancies have an increased likelihood of undergoing IOL postdate when recognized as postterm, hence making a calculation of the true gender distribution in prolonged pregnancy uncertain.

Male fetuses are already larger than females at the time of ultrasound dating, and are therefore at risk of being assigned a falsely longer gestation [Tunón *et al.*, 1998]. During this period of gestation the fetal BPD grows by an average of 0.44 mm per day [Persson *et al.*, 1978]. The method of adjustment of gestational age used in *Study I*, i.e., addition of 0.75 day in female-fetus pregnancies and subtraction of 0.75 day in male-fetus pregnancies, will then correspond to only 0.33 mm.

Obstetricians are inclined to induce labor in the postdate period because of a risk of an adverse perinatal outcome in prolonged pregnancy. To investigate whether such inductions are unnecessary or not was outside the scope of this study, but irrespective of whether the assigned gestational ages were falsely too long or falsely too short, it should be noted that even after adjustments for possible dating errors, both boys and girls born postterm had an increased risk of low Apgar scores compared with term pregnancies. The OR for girls having an Apgar score < 7 at 5 minutes was 2.8, whereas the corresponding figure for boys was 1.9. Although the difference was statistically not significant ( $P = 0.087$ ), we postulate that the underestimation of gestational age by 0.75 day in female-fetus pregnancies was likely to be the main cause of the observed difference. It may be estimated approximately that a difference of 0.75 day corresponds to a spontaneous onset of labor in 13-14 % of the postterm population; that is, this proportion of women carrying female fetuses on day 41+6 would not be recognized as postterm. This would imply that they may not be under the rigorous fetal surveillance routinely warranted.

It would thus seem justified to ask whether gestational age should be adjusted a second time, in the postdate period, when it is easier to accurately view the fetal genitalia by ultrasound. We do not believe this is feasible, however, since the risk associated with postdatism is a continuum that has already begun in the week following EDD. The key questions are whether a more vigilant fetal surveillance should be started earlier in the postdate period, and for how long an uncomplicated postdate pregnancy should be allowed to continue.

*Study I* did not address the possibility of influence of fetal gender differences on the identification of growth-restricted fetuses. Currently we are not using gender-specific growth charts. A difference of 0.75 day from the ‘true’ gestational age corresponds to a fetal growth of approximately 18 g (0.5 % of the mean birthweight) in an average-sized fetus at term according to our growth charts [Marsál *et al.*, 1996], which can be ignored from a clinical viewpoint. Using customized growth curves, Gardosi [1998] did not include fetal gender when calculating the optimum birthweight at term in early pregnancy, but when it is included, the deviation from the gender-unspecified mean weight at term will be less than 2 % (calculated from data by Gardosi *et al.* [1992], Wilcox *et al.* [1993] and West Midlands Perinatal Institute [2003]). This difference will mean that a fraction of pregnancies will be diagnosed as false positive or false negative for fetal growth restriction.

With the recent introduction of ultrasound measurement of nuchal translucency thickness [Nicolaidis *et al.*, 2000; Saltvedt *et al.*, 2006] and dating in the first trimester instead of the second, it can be expected that the measured gender-dependent differences in size will be smaller than with the current routine. First trimester ultrasound dating shows no gender-related difference in size [Selbing & McKay, 1985] and with this dating it can be anticipated that the skewed gender distribution in postterm pregnancy will decrease or even be erased.

## Starting fetal surveillance earlier in postterm pregnancy – a 15-year quasi-randomized controlled study (**Study II**)

We had the possibility of conducting a quasi-randomized controlled study, but with a retrospective design, to examine the question of whether, in postdate pregnancies, commencement of intensified fetal monitoring 1-3 days earlier than the postterm period could improve the short-term and long-term outcome in the offspring.

### **Results**

Details on pregnancy complications, and on the start of delivery, course of labor, perinatal outcome, morbidity and mortality are given in Table 1.

It was hypothesized that an earlier start of the initial routine postdate outpatient surveillance (Group A at 291-292 days, Group B at 293 days) would be more beneficial than starting at 294-295 days (Group C). Outcome parameters that were better in Group C than in Group A and/or group B are not commented on here. Of all parameters, only one was possibly in favor of an earlier start of the intensified fetal surveillance; namely in planned vaginal delivery, meconium stained amniotic fluid was more common in pregnancies where the initial monitoring was at 294-295 days (Group C, 29 %) than in pregnancies with the start at 291-292 days (Group A, 23 %) (Table 1). Of the total 6 cases with meconium aspiration syndrome, 5 belonged to group C, but the difference was not significant ( $P = 1.0$ ). The neonates hospitalized because of meconium aspiration syndrome were all discharged home healthy within 8-25 days.

In comparisons between postdates and term controls, long-term data did not indicate an increased risk of morbidity in the former group (Table 2). Children born postdate had fewer hospital admissions during childhood than those born at term. In particular, blood and respiratory disorders were less common among postdates.

The risk of an adverse outcome did not differ between the groups when composite grouping including mortality, meconium aspiration, neonatal convulsions, encephalopathy and brachial plexus injury was considered.

The higher rate of mortality in postterm pregnancies was solely due to a higher early neonatal death rate and no differences were seen between the different postterm groups (Table 2).

**Table 1.** Obstetric and neonatal outcome.

	Group A (n = 332)		Group B (n = 334)		Group C (n = 1366)		A vs. C		B vs. C		
							P	OR	95% CI	P	OR
Preeclampsia	7 (2)	14 (4)	35 (3)	0.8	0.82	0.36-1.86	0.2	1.66	0.88-3.13		
Oligohydramnios	65 (25)	73 (28)	221 (19)	0.2	1.26	0.93-1.71	0.02	1.45	1.08-1.95		
Non-reassuring nonstress test	2 (0.6)	0	5 (0.4)	0.9	1.65	0.32-8.54	0.6	-	-		
Blood flow changes*	1 (0.3)	0	0	0.4	-	-	-	-	-		
IUGR	15 (5)	13 (4)	3 (0.2)	<0.0005	21.50	6.19-74.71	<0.0005	18.40	5.21-64.95		
Elective cesarean section	6 (2)	6 (2)	32 (2)	0.7	0.77	0.32-1.85	0.7	0.76	0.32-1.84		
Spontaneous onset of labor	197 (60)	181 (55)	860 (64)	0.3	0.86	0.67-1.10	0.004	0.70	0.55-0.89		
normal vaginal delivery	158/197 (80)	127/181 (70)	663/860 (77)	0.4	1.20	0.82-1.77	0.06	0.70	0.49-1.0		
ventouse/forceps	22/197 (11)	26/181 (14)	80/860 (9)	0.5	1.23	0.74-2.02	0.06	1.64	1.02-2.63		
cesarean section	17/197 (9)	28/181 (15)	117/860 (14)	0.08	0.60	0.35-1.02	0.6	1.16	0.74-1.82		
Induction of labor	129 (40)	147 (45)	474 (36)	0.2	1.20	0.93-1.53	0.003	1.48	1.16-1.89		
normal vaginal delivery	77/129 (60)	94/147 (64)	298/474 (63)	0.6	0.87	0.58-1.30	0.9	1.05	0.71-1.54		
ventouse/forceps	16/129 (12)	14/147 (10)	62/474 (13)	1.0	0.94	0.52-1.69	0.3	0.70	0.38-1.29		
cesarean section	36/129 (28)	39/147 (27)	114/474 (24)	0.4	1.22	0.79-1.90	0.6	1.14	0.75-1.74		
Cesarean section	59/332 (18)	73/334 (22)	262/1366 (19)	0.6	0.91	0.67-1.24	0.3	1.18	0.88-1.58		
fetal distress	24/59 (41)	28/73 (38)	97/262 (37)	0.7	1.17	0.66-2.08	1.0	1.05	0.62-1.81		
failure to progress	18/59 (31)	21/73 (29)	89/262 (34)	0.7	0.85	0.46-1.57	0.5	0.79	0.45-1.38		
cephalopelvic disprop.	3/59 (5)	11/73 (15)	28/262 (11)	0.2	0.45	0.13-1.53	0.3	1.48	0.70-3.14		
maternal request	3/59 (5)	4/73 (5)	16/262 (6)	1.0	0.82	0.23-2.92	0.9	0.89	0.29-2.75		
failed induction	4/59 (7)	5/73 (7)	13/262 (5)	0.5	1.39	0.44-4.44	0.6	1.41	0.49-4.09		
large baby	3/59 (5)	4/73 (5)	17/262 (6)	1.0	0.77	0.22-2.73	1.0	0.84	0.27-2.56		
other reasons <sup>†</sup>	4/59 (7)	0	2/262 (0.4)	0.01	9.53	1.70-53.3	0.2	-	-		
Instrumental delivery	38/332 (11)	40/334 (12)	150/1366 (11)	0.9	1.05	0.72-1.53	0.7	1.10	0.76-1.60		
fetal distress	19/38 (50)	23/40 (58)	78/150 (52)	1.0	0.92	0.45-1.88	0.7	1.25	0.62-2.53		
failure to progress	18/38 (47)	16/40 (40)	64/150 (43)	0.7	1.21	0.59-2.47	0.9	0.9	0.44-1.82		
other indications	1/38 (3)	1/40 (3)	7/150 (5)	0.9	0.55	0.066-4.63	0.9	0.52	0.063-4.39		
Spontaneous normal vaginal delivery	235/332 (71)	221/334 (66)	954/1366 (70)	0.8	1.05	0.80-1.36	0.2	0.84	0.65-1.09		

Gestational age at delivery (d)	295.0 ± 3.0	295.7 ± 2.7	296.3 ± 11.6	<0.0001	-	-	<0.0001	-	-
Birthweight (g)	3911 ± 500	3955 ± 493	3925 ± 495	0.6	-	-	0.3	-	-
Birthweight deviation (%)	1.10 (12.4)	2.05 (12.5)	0.5 (12.6)	0.4	-	-	0.4	-	-0.06
SGA	8 (2)	6 (2)	23 (2)	0.5	1.44	0.64-3.25	0.9	1.07	0.43-2.64
LGA	14 (4)	18 (5)	63 (5)	0.9	0.91	0.50-1.65	0.6	1.10	0.69-2.02
Apgar score <7 at 5 min	9 (3)	8 (2)	28 (2)	0.6	1.33	0.62-2.85	0.9	1.08	0.60-1.93
Cord artery pH	7.21 ± 0.09	7.20 ± 0.06	7.20 ± 0.03	0.7	-	-	0.7	-	-
Cord vein pH	7.29 ± 0.86	7.29 ± 0.09	7.29 ± 0.09	0.8	-	-	0.8	-	-
Cord artery pH <7.06	15 (5)	15 (5)	57 (4)	0.9	1.09	0.61-1.94	0.9	1.08	0.60-1.93
Cord vein pH <7.15	17 (5)	16 (5)	67 (5)	1.0	1.04	0.61-1.81	1.0	1.04	0.60-1.70
Neonatal hypoglycemia	31 (9)	25 (8)	66 (5)	0.003	2.03	1.30-3.16	0.08	1.59	0.99-2.57
Meconium stained liquor <sup>†</sup>	75/326 (23)	82/328 (25)	383/1334 (29)	0.05	0.75	0.56-0.99	0.2	0.84	0.63-1.09
Thick meconium <sup>‡</sup>	31/326 (10)	42/328 (13)	143/1334 (11)	0.6	0.88	0.58-1.32	0.3	1.22	0.85-1.77
Meconium aspiration	1 (0.3)	0	5 (0.4)	1.0	0.82	0.096-7.06	0.6	-	-
Respiratory distress	31 (9)	12 (4)	34 (3)	<0.0005	4.03	2.44-6.67	0.4	1.46	0.75-2.85
Brachial plexus injury	1 (0.3)	2 (0.6)	5 (0.4)	1.0	0.82	0.096-7.06	0.6	1.64	0.32-8.49
Convulsions	0	0	3 (2)	1.0	-	-	1.0	-	-
Neonatal encephalopathy <sup>§</sup>	1 (0.3)	2 (0.6)	1 (0.1)	0.4	4.12	0.26-66.11	0.1	8.22	0.74-90.96
Intracerebral bleeding	0	0	0	-	-	-	-	-	-
Transfer to NICU	25 (8)	18 (5)	87 (6)	0.5	1.20	0.75-1.90	0.6	0.84	0.50-1.41
Mortality <sup>μ</sup>	2 (0.6)	1 (0.3)	6 (0.4)	1.0	1.37	0.28-6.84	0.9	1.37	0.27-6.80

\* Pathological Doppler velocimetry in the umbilical artery.

<sup>†</sup> In group A ablatio placentae, previous stillbirth, IUGR, previous cesarean section, and in group C ablatio placentae, IUGR

<sup>‡</sup> Cases with elective cesarean section excluded.

<sup>§</sup> Cases reported between January 1998 and October 2005. Encephalopathy diagnoses not reported before 1998.

<sup>μ</sup> Includes intrauterine fetal death, mortality during birth, and mortality up to one year after delivery.

**Table 2.** Total morbidity (as hospital admissions) and mortality in children born postterm compared to controls during the period 1990-2004.

	Group A n = 287	Group B n = 299	Group C n = 1210	Controls n = 11784	A vs. controls P	B vs. controls P	C vs. controls P	A+B+C vs. controls P
<b>MORBIDITY</b>								
<b>Hospitalization</b>								
No admissions	202 (70.4)	205 (68.6)	761 (62.9)	7397 (62.8)	0.01	0.05	1.0	0.07
1-5 times	84 (29.3)	91 (30.4)	434 (35.9)	4247 (36.0)	0.02	0.05	0.9	0.09
6-10 times	1 (0.3)	2 (0.7)	11 (0.9)	91 (0.8)	0.7	1.0	0.7	0.9
> 11 times	0	1 (0.3)	4 (0.3)	49 (0.4)	0.6	1.0	0.8	0.5
<b>MORTALITY</b>								
IUFD*	0	0	1 (0.1)	-	-	-	-	-
During labor	0	0	1 (0.1)	2 (0.0)	1.0	1.0	0.3	0.3
Death within 0-6 (d)	2 (0.7)	1(0.3)	3 (0.2)	0	0.0006	0.03	0.0008	0.000005
Death within 7-27 (d)	0	0	0	4 (0.0)	1.0	1.0	1.0	1.0
Death within 28-364 (d)	0	0	1 (0.1)	12 (0.1)	1.0	1.0	0.6	1.0
Death after 1 year	0	0	0	2 (0.0)	1.0	1.0	1.0	1.0
Children alive	285 (99.3)	298 (99.7)	1205 (99.6)	11764 (99.8)	0.09	0.4	0.08	0.02†

\* Intrauterine fetal death was exclusion criterion in the control term group. In Group C, one case of IUFD in 2005 was not included (period 1990-2004 shown in table)

† Risk of death, postterm vs. term, OR 2.63, 95 % CI 1.16-5.98.

## Comments

*Study II* showed that commencement of intensified fetal and maternal surveillance 1-3 days earlier than at 294 days does not improve the outcome, either in the short-term or the long-term perspective. No difference in either neonatal mortality or neonatal morbidity in favor of an earlier start of postdate check-ups was found. In fact, the only possibly unfavorable finding in the group with initial monitoring at 294-295 days was that meconium stained amniotic fluid was more common than in the group starting at 291-292 days, and that five of the total six neonates with meconium aspiration belonged to in the former group. Despite a study period of 15 years, the study was grossly underpowered to show a significant difference. However, the study had a 90 % power to show an OR of 1.1 for hospital admission during childhood.

There are studies indicating that the risk of perinatal morbidity, including fetal distress and asphyxia, meconium aspiration, birth trauma, and neonatal convulsions, increases with each week beyond 40 weeks [Grausz & Heimler, 1983; Arias, 1987]. However, neither short-term nor long-term morbidity data from *Study II* support these findings. On the contrary, there was a trend towards lower long-term morbidity in practically all organ systems among children born postterm.

Not unexpected, the mortality figures were higher in postterm than in term pregnancy. This was solely due to a difference in early neonatal deaths. However, these deaths could not have been prevented by earlier check-ups, since the women had, in fact, been for postterm check-ups repeatedly, and the causes of the deaths were not related to gestational length but mainly to intrapartum asphyxia.

The efficacy of starting postterm antenatal testing at 41 in stead of 42 weeks is controversial. A protocol for postdate pregnancy management is largely dependent on the available resources, both in the case of an active and of a conservative attitude. A start of intensified surveillance at 41+0 weeks would involve 23 % of our total pregnant population, and with a start at 41+3 weeks this figure would be 14 % [Ingemarsson, 2000]. With routine ultrasound dating in the early second trimester, the incidence of postterm pregnancy in Malmö is currently 4 %. Since the intrauterine fetal deaths (IUFDs) that are potentially avoidable with an earlier start of the intensified surveillance are very few, the efforts required for each prevented IUFD would be extremely large. Ingemarsson & Källén [1997] found a postterm IUFD rate among nulliparae of 2.26/1000 compared to 1.23/1000 at term



(although among multiparae it was not increased). To demonstrate, in a prospective randomized controlled trial, a decline of the fetal death rate from 2.26/1000 to 1.23/1000 (at an  $\alpha = 0.05$  and  $\beta = 0.20$ ), as a result of commencement of an interventional policy at an earlier gestational age, 25772 cases in each arm would be needed. Such a study is of course not feasible.

Two decades ago, Steer [1986] commented that the excess mortality in postterm pregnancy amounted to less than 5 % of the total perinatal mortality, and that it was only half that at 37 weeks. He questioned the appropriateness of the high IOL rate in uncomplicated postterm pregnancies and emphasized the need for vigilance for signs of IUGR throughout pregnancy. The identification of IUGR is of paramount importance for a good perinatal outcome [Lindqvist & Molin, 2005], and in such cases otherwise uncomplicated postterm pregnancies can safely be allowed to await spontaneous labor under close fetal surveillance, even when 43+ weeks have been reached [Olofsson & Saldeen, 1996].

### **Fetal surveillance in postterm pregnancy: The contribution of middle cerebral artery Doppler flow velocimetry (*Study III*)**

The question addressed in this study was whether addition of fetal MCA Doppler velocimetry to a routine postterm pregnancy surveillance program would improve the outcome.

#### **Results**

In 33 women (14 %) there were indications for termination of the pregnancy: by IOL in 88 % and by elective CS in 12 %. The remaining 196 women (86 %) were initially managed conservatively. In 32 cases (16 %) of the conservatively managed cases some problem indicating elective termination of the pregnancy subsequently developed. In addition, in 41 cases (21 %) IOL was performed only on the indication postterm pregnancy.

Women in the electively terminated group had an operative delivery rate of 42 %, compared to 27 % in the conservatively managed group (difference not

significant). No neonatal distress occurred in the electively terminated group, but this was noted in 12 % of the conservatively managed cases (Fisher's exact test;  $P = 0.053$ ). No other outcome measures were worse in the conservative group (outcome measures as shown in Table 3).

Altogether 17 fetuses (7 %) had an MCA PI  $< 0.80$ , indicating brain-sparing flow (BSF). There was no difference in the distribution of BSF between the electively terminated group (4/33, 12 %) and the conservative group (13/196, 7 %). Significantly more pregnancies were terminated by CS in the BSF group (41 % vs. 16 %;  $P = 0.02$ ), mainly with emergency CS (35 % vs. 14 %;  $P = 0.04$ ), but none of the 13 'conservatively managed BSF' neonates had a low Apgar score, had a low cord blood pH, were SGA, had meconium aspiration syndrome or neonatal distress, or were transferred to the NICU. Overall, none of the 17 neonates with BSF had an adverse perinatal outcome.

**Table 3.** Cerebroplacental ratio (CPR) defined as middle cerebral artery (MCA) PI to umbilical artery (UA) PI ratio. The cut-off limit for CPR at 294 days was 0.82.

CPR	$< 0.82$	$\geq 0.82$	$< 0.82$ vs. $\geq 0.82$		
	(n = 7)	(n = 222)	P	OR	95 % CI
Gender, boy	3 (43)	142 (64)	0.3	0.42	0.092-1.94
Induction of labor	2 (14)	100 (45)	0.5	0.49	0.093-2.57
Oligohydramnios	0	38 (17)	0.6	-	-
IUGR	0	9 (4)	1.0	-	-
Pathological blood flow in UA	1 (14)	3 (0.5)	0.1	12.17	1.1-134.
Failure to progress	0	26 (12)	1.0	-	-
Gestational age at delivery (d)	296.4 $\pm$ 1.1	297.1 $\pm$ 2.3	0.5	-	-
Normal vaginal delivery	6 (86)	153 (69)	0.7	2.71	0.32-22.91
Ventouse/forceps	1 (14)	30 (14)	1.0	1.067	0.12-9.17
Cesarean section	1 (14)	39 (18)	1.0	0.78	0.092-6.68
Neonatal distress	0	11 (5)	1.0	-	-
Apgar score 5-min $< 7$	0	1 (0.5)	1.0	-	-
pHa $< 7.06$	0	5 (2)	1.0	-	-
pHv $< 7.15$	0	7 (3)	1.0	-	-
Birthweight (g)	3780 $\pm$ 613	3856 $\pm$ 443	0.9	-	-
Weight deviation $> - 22\%$	0	3 (1)	1.0	-	-
Meconium stained liquor	0/7	40/218 (18)	0.4	-	-
Meconium aspiration	0	0	-	-	-
Transfer to NICU	1	5 (2)	0.2	7.23	0.73-71.80

The BSF phenomenon was also evaluated according to the definition of a low CPR ( $< 0.82$ ), which occurred in 7 fetuses (3 %). In comparison with the 222 cases with a CPR  $\geq 0.82$ , no significant differences in the evaluated parameters were found (Table 3).

Childhood morbidity data obtained from the national Patient Register did not show any differences between neonates with and without BSF. When the children had reached the age of 10-14 years, 59 % and 47 % of them, respectively, had been admitted to hospital. No deaths occurred in the BSF group, whereas one fetus in the non-BSF group died of asphyxia during labor

### **Comments**

The managing obstetricians were blinded to the results of the MCA Doppler examinations, and in a hypothetical intention-to-treat manner we assessed what fetal MCA Doppler velocimetry could have added to the management with respect to neonatal and long-term outcomes. *Study III* showed that detecting BSF had no additional benefit in a routine fetal surveillance program of postterm pregnancy already including NST, UA Doppler velocimetry, and ultrasound with fetal growth and amniotic fluid volume estimations.

BSF occurred in 7 % of the cases, predominantly among those managed conservatively, as other surveillance methods tested negative in BSF cases. Irrespective of whether the management was active or expectant, no neonate with BSF had an adverse neonatal outcome.

Several studies have indicated an increased rate of adverse perinatal outcomes in postterm fetuses with BSF [Anteby *et al.*, 1994; Devine *et al.*, 1994; Bar-Hava *et al.*, 1995; Dubiel *et al.*, 1996; Selam *et al.*, 2000; Lam *et al.*, 2005]. This was not confirmed in *Study III*. In fact, only in 2 of the 13 cases with BSF in the conservatively managed group developed complications (oligohydramnios) necessitating IOL.

There are some methodological aspects to consider when assessing and comparing results from different studies regarding the value of cerebral blood flow recordings in postterm pregnancy. Some of these aspects are compiled in a summarized literature overview presented in Table 4.

**Table 4.** Studies of fetal cerebral blood flow in postterm pregnancies ( $\geq 41$  weeks of gestation).

Reference	(n), GA range	Cerebral vessel	Results and measure endpoint
Brar <i>et al.</i> , [1989]	45, $\geq 41$ w	Carotid artery	A low PI, associated with FD
Arduini <i>et al.</i> , [1990]	45, $> 42$ w	Carotid artery	A high PI during maternal hyperoxygenation
Battaglia <i>et al.</i> , [1991]	82, $\geq 41$ w	MCA	Abnormal flow was not predictive on perinatal outcome, same range for 41 w or more
Malcus <i>et al.</i> , [1991]	102, $> 42$ w	Carotid artery	Abnormal flow was not predictive on perinatal outcome
Gramellini <i>et al.</i> , [1992]	45, 30-41 w	MCA	CPR PI better predictor of SGA and adverse perinatal outcome than MCA or UA alone, same range for 39-41 w
Anteby <i>et al.</i> , [1994]	78, 41-42 w	MCA	A low PI, but not S/D ratio in MCA, associated with FD, same range for 41 w or more
Devine <i>et al.</i> , [1994]	49, $\geq 41$ w	MCA	A low CPR PI associated with FD, single cut-off MCA/UA $< 1.05$
Bar-Hava <i>et al.</i> , [1995]	42, $\geq 41$ w	MCA	No difference in RI between cases with or without oligohydranmiosis, but lower birthweight in the first
Zimmerman <i>et al.</i> , [1995]	153, $\geq 41$ w	MCA	No significant RI change with increasing gestational age
Dubiel <i>et al.</i> , [1997]	50, $\geq 42$ w	MCA	Low MCA PI associated with SGA and low AFI, different index <sup>a</sup>
Kurmanavicius <i>et al.</i> , [1997]	1675, 24-42 w	MCA	Reference values for MCA, but 95 <sup>th</sup> centile was not calculated
Selam <i>et al.</i> , [2000]	28, $\geq 41$ w	MCA	Low MCA PI in cases with oligohydranmiosis, same range for 41 or more
Figueras <i>et al.</i> , [2004]	77, 41-42 w	MCA	Proximal MCA PI predicts umbilical cord pO <sub>2</sub> and occurrence of cesarean section, different sites of MCA
Palacio <i>et al.</i> , [2004]	140, 41-42 w	MCA	Reference values for MCA
Lam <i>et al.</i> , [2005]	118, $\geq 41$ w	MCA	Low MCA PI better predictor of risk for meconiumstained liquor than AFI

a) BSF when MCA PI  $< 0.75$ , MCA mean velocity  $> 50$ cm/s and MCA/UA PI  $< 1.08$ .

Doppler recordings in both the internal carotid artery and the MCA have been used to assess the fetal cerebral circulation. In the MCA, the Doppler sampling volume has been placed in the proximal, middle, or distal part of the vessel. Moreover, either the resistance index or PI has been used to describe the peripheral vascular resistance. A source of significant confounding is that different cutoffs of MCA PI to describe BSF have been in use, mostly without reference to postterm pregnancy. In *Study III*, we based the definitions of BSF on recently published gestational age-adjusted reference ranges, with MCA PI < 0.80 or CPR < 0.82 considered abnormal at and beyond 42 weeks [Palacio *et al.*, 2004].

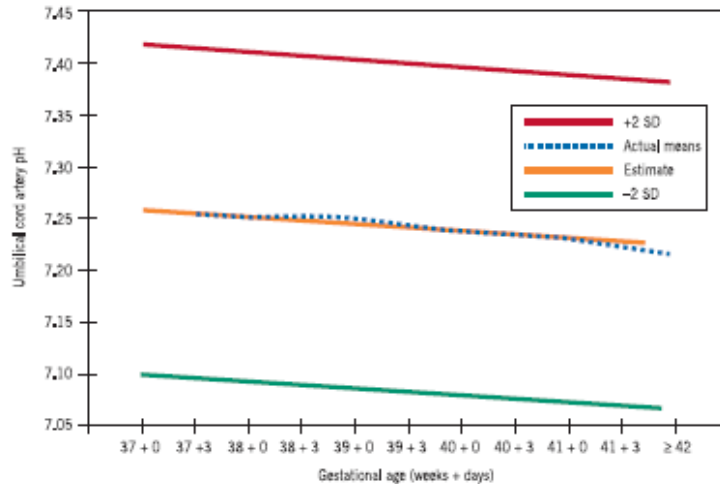
We found no association between BSF and an adverse neonatal or childhood outcome in postterm pregnancy. Morbidity data obtained from national registers based on hospital admissions showed no differences in long-term outcome between fetuses with and without BSF, and the mortality in the BSF group was nil. This suggests that there is no need to add MCA Doppler flow velocimetry to the current routine management program.

### Gestational age-dependent reference values for pH in umbilical cord arterial blood at term (**Study IV**)

The aims of this study were twofold. Firstly, to define the reference intervals of pH in arterial cord blood as a function of gestational age in alert newborns at term. Secondly, to compare the association between Apgar score and pH with use of a stationary definition of cord acidemia and of a gestational age-adjusted definition of a low pH.

#### **Results**

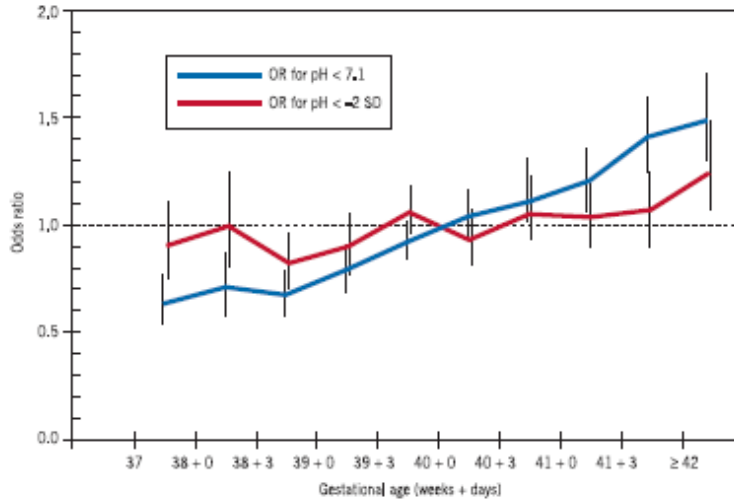
A negative linear relationship between cord artery pH and gestational age was found, with a mean (SD) cord artery pH of 7.26 (0.08) at 37 weeks and of 7.22 (0.08) at 42+ weeks (Fig. 6). The cutoff values for definition of cord blood acidemia, representing the mean value – 2 SD, were 7.10 at 37 weeks and 7.06 in postterm babies.



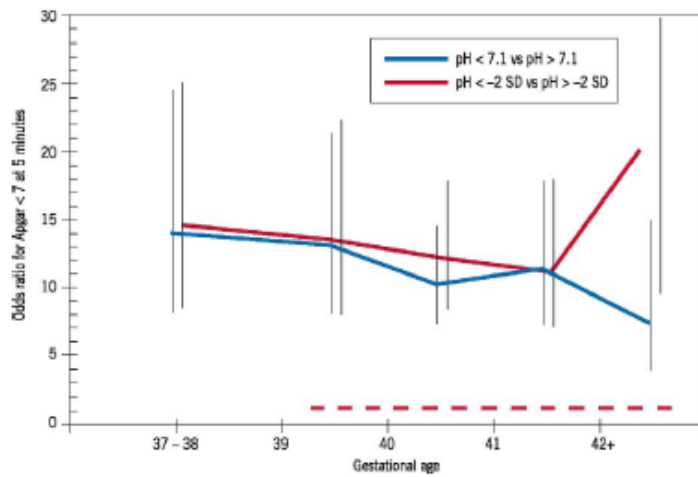
**Figure 6.** Umbilical cord artery pH relative to gestational age in 24390 alert newborns.

The OR for a pH of less than 7.10 increased continuously throughout the term period, from 0.6 at 37 weeks to 1.5 at 42 weeks, irrespective of whether metabolic acidosis was present or not (Fig. 6). The OR for a pH below 7.10 among infants with metabolic acidosis born postterm was 1.63 (95 % CI = 1.37–1.93) and among infants without metabolic acidosis 1.25 (95 % CI = 0.98-1.59). In contrast, the OR for a low pH according to the gestational age-dependent definition of less than the mean – 2 SD was steady and a significant increase was not observed before the postterm period (OR = 1.24, 95 % CI = 1.05-1.47). With stationary pH references, acidemia was falsely assigned in 25 % (670/2623) of newborns during week 37+0 to 41+6 and in 35 % (89/249) of postterms (Fig. 7).

To assess the risk of a suboptimal outcome relative to a low cord pH when using the two different definitions of cord blood acidemia, the OR for a 5-minute Apgar score of less than 7 was calculated. A linear decrease of the association between Apgar score < 7 at 5 minutes and pH < 7.10 with increasing duration of pregnancy was indicated, but the results were not significant ( $P$  for linear trend = 0.097). The results were similar for pH less than the mean - 2 SD during the term period, but postterm there was no indication of an association between low Apgar score and low pH (Fig. 8).



**Figure 7.** Gestational age as a risk factor for umbilical cord artery pH less than 7.10 and pH less than (mean – 2 standard deviations).



**Figure 8.** The risk of an Apgar score less than 7 at 5 minutes relative to gestational age in newborns with an umbilical cord artery pH less than 7.10 and/or less than (mean – 2 standard deviation), respectively.

### **Comments**

A stationary pH cutoff at 7.10 has commonly been used in Sweden for some decades to describe fetal acidemia. In 1997, in a very large series of cases, Herbst *et al.* found that a pH of 7.10 corresponds to the mean value – 2 SD in term deliveries. However, *Study IV* strongly confirmed previous findings that the umbilical cord artery pH at birth decreases physiologically with advancing gestational age [Nicolaides *et al.*, 1989; Weiner *et al.*, 1992; Helwig *et al.*, 1996; Wiberg *et al.*, 2006a]. The gestational age-adjusted lower pH cutoff was superior to the stationary definition of cord acidemia in reflecting the newborn's vitality, suggesting that a cutoff at pH 7.06 should be used in postterm pregnancy.

Although the pH reflects a biochemical course of events and the Apgar score represents the newborn's vitality and alertness, these two outcome variables are expected to perform in parallel. In contrast to the OR trend curve for a pH less than 7.10, the risk of having a 5-minute Apgar score below 7 was independent of gestational age and did not increase until the postterm period. At a stationary cutoff at pH < 7.10, the Apgar score < 7 OR trend curve showed a linear decrease with gestational age. This means that with a stationary definition of acidemia the risk of having a low Apgar score in acidemic newborns should decline with gestational age. As this finding seemed paradoxical, we subsequently analyzed the same association when using a gestational age-adjusted definition of a low pH (i.e., less than 2 SD) and found that during the term period the Apgar score < 7 OR trend curve showed no association with gestational age. The gestational age-dependent pH cutoff value thus proved better able to reflect a pathophysiological course of events when expressed in terms of a low Apgar score.

The findings in *Study IV* suggest that even within the narrow 5-week period of term pregnancy, significant biochemical changes take place. *Study IV* showed that 25 % of newborns with a cord artery pH of less than 7.10 at term, and 35 % of those postterm, will be given with a diagnosis of cord blood acidemia despite having a pH within the gestational age-adjusted reference range of mean  $\pm$  2 SD. Thus, the correctness of using a stationary cord artery pH cutoff as an index of a suboptimal fetal outcome must be questioned. A gestational age-adjusted pH cutoff will provide a more true measure of the newborn's acid-base status.



The physiological mechanisms underlying the continuous decrease in fetal pH are only partly known. Simultaneously with a declining umbilical cord artery pH, the cord arterial carbon dioxide partial pressure (pCO<sub>2</sub>) and base deficit increase and the bicarbonate level decreases with advancing gestational age [Wiberg *et al.*, 2006a,b]. A mixed respiratory and metabolic acidemia develops in umbilical arterial blood with increasing gestational age, where the respiratory component is caused by an increased 'carbon dioxide load' from the growing fetus, while the etiology of the metabolic component, as revealed by an increasing base deficit, is as yet unknown [Wiberg *et al.*, 2006a,b].

## SUMMARY AND CONCLUSIONS

### **Study I**

This study on ultrasound dating of 82484 singleton pregnancies in the early second trimester showed that male fetuses are over-represented in postterm pregnancies. As a result of a gender-dependent difference in size, corresponding to 1.5 gestational days, male-fetus pregnancies are assigned a falsely too long, and female-fetus pregnancies a falsely too short gestational length at ultrasound dating. By adjustment of gestational length by  $\pm 0.75$  day (in practice, 3 of 4 cases were adjusted by  $\pm 1$  day), the increased chance of having a boy in postterm pregnancy was reduced from an OR of 1.41 (95 % CI = 1.33-1.49) to 0.90 (95 % CI = 0.84-0.95).

Male-fetus pregnancies were at an increased risk of having induction of labor postdate when recognized as postterm according to the ultrasound dating. No gender difference in the rate of IOL was found after adjustment for the size difference.

Both male and female postterm newborns were at increased risk of having a low Apgar score compared with newborns in term pregnancies. The risk was higher among females than among males, but the difference was not significant ( $P = 0.087$ ).

An underestimation of gestational length by 0.75 day in female-fetus pregnancies corresponds to a spontaneous onset of labor in 13-14 % of the postterm population; that is, this proportion of women carrying female fetuses on day 41+6 is not recognized as being postterm. These women may hence not undergo the vigilant control warranted.

### **Conclusion**

A skewed gender distribution in postterm pregnancy results in a higher rate of labor induction in male-fetus pregnancies at 41+ weeks, and there is a trend among postterm newborns that more girls than boys have a low Apgar score.

## **Study II**

This quasi-randomized controlled trial on 2032 antenatally uncomplicated postdate/postterm pregnancies during a 15-year period showed that commencement of an intensified fetal and maternal surveillance 1-3 days earlier than at 294 days did not result in better outcomes, either in the short-term or the long-term perspective.

The only possibly unfavorable outcome parameter in the group commencing monitoring at 294-295 days was that meconium stained amniotic fluid was more common than in the group starting at 291-292 days (29 % vs. 23 %,  $P = 0.053$ ). However, neonatal meconium aspiration syndrome occurred at a frequency of only 3/1000 and there was no difference between the groups.

In a comparison between the postterm neonates and 11764 controls, which were delivered at 40+0 weeks  $\pm 3$  days, long-term data did not indicate an increased risk of morbidity among the postterms. Children born postterm did not have more hospital admissions than those born at term. On the contrary, postterms had fewer admissions for disorders of practically all organ systems (35 % vs. 37 %,  $P = 0.07$ ).

The higher rate of total mortality among postterm pregnancies (4.5/1000) compared to controls (1.7/1000) was entirely attributable to a higher early neonatal death rate (3.3/1000 vs. nil). Since the postterm early neonatal deaths were mainly due to intrapartum asphyxia, and the women were already under close fetal surveillance, an earlier start of an intensified surveillance would have made no difference. Between the different postterm groups, there was no difference in mortality.

## **Conclusion**

Starting intensified fetal surveillance early or late in the interval 291-295 gestational days makes no difference with regard to neonatal and childhood morbidity in otherwise uncomplicated postterm pregnancies.

## **Study III**

In this observational study on 229 postterm pregnancies, with the managing obstetricians blinded to the results of Doppler ultrasound flow velocimetry in

the fetal middle cerebral artery, detection of a brain-sparing flow would have had little to add in a postterm pregnancy surveillance program already including the nonstress test, umbilical artery Doppler flow velocimetry, and ultrasound for estimation of fetal growth and amniotic fluid volume. Neither the neonatal nor the long-term outcome was impaired in children with brain-sparing flow during fetal life. Brain-sparing flow occurred in 7 % of postterm fetuses, but was not associated with an adverse outcome in a single case. Childhood morbidity data did not show any differences between neonates with and without brain-sparing flow, and the mortality in the brain-sparing flow group was nil.

Fetal growth restriction was suspected in 29 % of fetuses with brain-sparing flow, but the true incidence of SGA was only 6 %. A suspicion of growth restriction will influence the obstetrician in charge in the direction of more active management, which may explain the higher cesarean section rate in the brain-sparing flow group.

### **Conclusion**

From an intention-to-treat perspective, addition of fetal middle cerebral artery Doppler velocimetry to an already vigilant postterm pregnancy surveillance program would be of little benefit.

### **Study IV**

To create a gestational age-adjusted reference curve, values of umbilical cord artery pH in 24390 vigorous newborns between 37 and 42+ weeks were related to gestational age. The pH decreased linearly with advancing gestational age, with the lower reference limit (mean minus 2 standard deviations) corresponding to a pH of 7.10 at 37 weeks and 7.06 at 42 weeks.

When the gestational age-adjusted pH values were compared with a stationary cutoff at pH < 7.10 in 44978 newborns, the stationary cutoff resulted in a false positive diagnosis of acidemia in 25 % of term newborns and in 35 % of postterm newborns.

Although the pH reflects a biochemical course of events and the Apgar score the newborn's vitality and alertness, these two outcome parameters are

### *Summary and Conclusion*

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expected to perform in parallel. However, at a stationary cutoff at pH < 7.10 the odds ratio trend curve for an Apgar score < 7 showed a linear decrease with gestational age. The interpretation of this is that with a stationary definition of acidemia the risk of a low Apgar score in acidemic newborns decreases with gestational age. This seemingly nonphysiological finding was eliminated when a cutoff corresponding to the mean minus 2 standard deviations was used instead. This observation suggests that a gestational age-dependent pH cutoff is better than a stationary cutoff for reflecting depression of the newborn's vitality.

### **Conclusion**

The umbilical artery pH at birth shows a physiological linear decline with advancing gestational age. Gestational age-adjusted reference values, corresponding to the mean  $\pm$  2 standard deviations, result in fewer diagnoses of cord acidemia than a stationary cutoff at a pH of less than 7.10.

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## POPULÄRVETENSKAPLIG SAMMANFATTNING

### PÅ SVENSKA

I Sverige dateras 98 % av alla graviditeter vid en ultraljudsundersökning tidigt i den andra trimestern och dagen då graviditeten är fullgången, d.v.s. beräknad förlossningsdag, fastställs då. Fyrtio fullgångna veckor har då förflutit, betecknat som 40 fulla veckor och 0 dagar (40+0, motsvarande 280 dagar). En annan beteckning är att säga att graviditeten är vid termin. Om kvinnan förblir oförlöst 2 veckor efter beräknad tidpunkt för nedkomst (42+0, 294 dagar) benämns graviditeten som överburen. Fördelen med att beräkna graviditetslängden med ultraljud och inte räkna efter den senaste menstruationen är att beräkningen blir säkrare, med en överburenhetsfrekvens på 4-7 % i stället för 9-10 %.

Det är sedan länge känt att kurvorna för perinatal dödlighet och sjuklighet båda beskriver ett U-format förlopp i förhållande till graviditetslängden, med sin lägsta punkt vid 40 veckor. Förtidsbörd och överburenhet innebär således ökad risk jämfört med förlossning vid termin. Komplikationerna vid överburenhet är, förutom en ökad dödlighet, bl.a. också en ökad risk för mekoniumaspiration med svåra andningsproblem som följd, förlossningskada p.g.a. barnets ökade storlek, samt kramper i nyföddhetsperioden.

Inom graviditets- och förlossningsvården läggs stor möda vid att minska riskerna för komplikationer vid överburenhet. Till skillnad från förtidsbörd, där kvinnan ofta kommer till förlossningsavdelningen med pågående värkar, är det vid överburenhet möjligt för den medicinska professionen att nedbringa komplikationsrisken. Målet är då att identifiera riskfallen och elektivt förlösa dessa kvinnor, medan kvinnor utan komplikationer kan fortsätta sin graviditet under intensifierad övervakning. Utomlands är det vanligt att man helt enkelt inducerar förlossningsarbetet hos alla som passerat 41 veckor, eller ännu tidigare. Den konservativa linjen är emellertid allmänt rådande i Sverige, eftersom man då låter förlossningen komma spontant igång och därmed minskar risken för komplikation enbart p.g.a. att man intervenerar. Med en konservativ handläggning kan man förvänta sig att hälften av alla överburna kvinnor är i spontant förlossningsarbete inom 3 dagar.

Överburenhet är ett i obstetriska sammanhang relativt sent uppmärksammat problem och många delar av den kliniska handläggningen är därför kontroversiell eller oklar. I den föreliggande avhandlingen belyses några kliniskt viktiga aspekter på överburenhet: (1) betydelsen i överburen tid av en falskt för lång beräknad graviditetslängd hos pojkfoster, respektive falskt för kort hos flickfoster, beroende på att man inte tar hänsyn till en storleksskillnad mellan könen redan vid ultraljudsdatering i andra trimestern; (2) betydelsen av en tidigare påbörjad intensifierad fosterövervakning vid överburenhet; (3) den potentiella nyttan med att använda cerebralt blodflöde och diagnostik av brain-sparing blodflöde som övervakningsinstrument vid överburenhet; och (4) en fysiologisk utveckling av "acidemi" hos fostret med ökande graviditetslängd och dess betydelse då pH i navelsträngsblod används som perinatal utfallspareter.

Studierna bygger huvudsakligen på uppgifter hämtade ur databaserade register vid Kvinnokliniken i Malmö (MacOB), södra sjukvårdsregionen (Perinatal Revision Syd), Medicinskt Födelseregister, Dödsfallsregistret och Patientregistret. Många uppgifter i MacOB och Perinatal Revision Syd är införda i forskningssyfte.

Det **första delarbetet** handlar om de kliniska konsekvenserna av att alla foster bedöms som lika stora vid ultraljudsdatering i den andra trimestern. Man har tidigare ansett att skillnaden mellan pojk- och flickfoster, motsvarande 1,5 dagars graviditetslängd i ett svenskt material, saknar klinisk betydelse. I ett material omfattande 82.484 fullgångna barn födda vid 11 sjukhus i södra Sverige fann vi en överrepresentation av pojkar vid överburenhet (OR 1,41). Att pojkar är vanligare vid överburenhet är känt sedan tidigare och den kliniska betydelsen av fyndet är tveksam. Beträffande flickor så var risken för låg Apgar-poäng vid födelsen högre än hos pojkar, men skillnaden kunde inte fastställas statistiskt ( $P = 0,087$ ).

I det **andra delarbetet** utvärderade vi huruvida en tidigareläggning av "överburenhetskontrollerna" skulle kunna minska morbiditet och mortalitet, inte bara i ett korttidsperspektiv utan även i ett långtidsperspektiv. Under snart två decennier har överburenhet handlagts på ett nästan oförändrat sätt i Malmö. Vi har följt en handläggning där en intensifierad övervakning med klinisk värdering, ultraljud för tillväxtkontroll, mätning av fostervattenmängden, CTG och blodflöde i navelsträngsartären gjorts strikt i vecka 42+0, d.v.s. på dagen för när överburenhet börjar enligt definitionen. En tidigareläggning skulle medföra ökad arbetsbelastning och en senareläggning en ökad risk för barnet. Laboratorierna för

ultraljud och blodflödesmätningar är emellertid stängda på helger och helgdagar, och kvinnor som blir överburna under dessa tider har då kontrollerats på föregående fredag, d.v.s. i vecka 41+6 eller 41+5. I vissa fall har kontrollen skett vecka 41+4 eller 42+1. Eftersom vi mycket noggrant har noterat i databasen vilken graviditetsdag ultraljud- och blodflödeskontrollerna skett, och på vilken indikation ("överburenhetskontroll"), har vi nu på ett kvasi-randomiserat sätt kunnat bedöma skillnader i utfall om kontrollen gjorts i vecka 41+4-5, 41+6, eller 42+0-1. 2.032 fall har under perioden 1990-2005 kontrollerats på detta sätt. Vi fann att en tidigareläggning gjorde ingen skillnad i utfall. Detta kan bero bl.a. på att mödravården är så pass effektiv i att hitta komplikationer så att de graviditeter som går till överburen tid är oftare än genomsnittet okomplicerade. Vi gjorde därför en jämförelse med en kontrollgrupp på 11.784 kvinnor med okomplicerade graviditeter med förlossning vecka 40+0 ± 3 dagar. Jämförelsen gjordes med uppgifter från Patientregistret och Dödsfallsregistret. Vi fann, som väntat, att perinatalmortaliteten i överburenhetsgruppen var högre, men oväntat, att morbiditeten under barndomen var lägre.

I det *tredje delarbetet* värderades vilken nytta man skulle kunna ha av att rutinmässigt utföra i blodflödesmätningar i mellersta cerebraltären hos fostret vid överburenhet. Under perioden 1992-96 genomgick 229 överburna kvinnor rutinundersökning kompletterad med blodflödesundersökning i mellersta cerebraltären. Resultatet av den senare undersökningen rapporterades inte till handläggande kliniker. Placentainsufficiens är, åtminstone enligt äldre litteratur, en väntad komplikation vid överburenhet, och placentainsufficiens kan medföra dålig fostertillväxt och/eller fetal hypoxemi, vilket i sin tur medför att fostret kompenserar för en dålig syresättning genom att omdirigera blodflödet till prioriterade organ såsom hjärna, hjärta och binjurar. En redistribution av blodflödet till hjärnan kallas brain-sparing och innebär att det perifera vaskulära flödesmotståndet minskar i cerebrala artärer. Flödesmotståndet kan lätt mätas med Doppler-ultraljudteknik i mellersta cerebraltären. Utifrån vad det rutinmässiga undersökningsprogrammet med CTG, ultraljud, fostervattenmängd, blodflöde i navelsträngsartären, blodtrycksmätning, urinsticka, etc., identifierade, värderade vi i vilken mån brain-sparing-flöde i f.f.a gruppen som handlagts konservativt skulle kunna ha bidragit med för att förhindra eller lindra en komplikation hos barnet. Vi fann att cerebral blodflödesmätning skulle inte ha medfört någon förbättring, men å andra sidan fanns det inga sjuka eller påverkade barn bland dem som hade brain-sparing som foster (17 st, 7 %). En uppföljning med data från Patientregistret



visade ingen skillnad i morbiditet under barndomen mellan de som hade haft eller inte haft brain-sparing-flöde som foster.

Det **fjärde delarbetet** berör pH i arteriellt navelsträngsblod som obstetrisk kvalitetsparameter. Blodgaser i navelsträngsblod används (A) kliniskt för bedömning av fosterpåverkan i individuella fall, (B) som obstetrisk kvalitetsparameter i förlossningsvården, och (C) som utfallsparameter i klinisk forskning. Traditionellt har ett  $\text{pH} < 7,10$  använts som indicium på acidosis, men eftersom pH sjunker med graviditetslängden ger ett sådant stationärt gränsvärde en falsk bild av morbiditet. Referensvärden för pH i arteriellt navelsträngsblod bestämdes hos 24.390 alerta nyfödda i graviditetsvecka 37 till 42+. pH sjunker då linjärt med graviditetslängden. OR för  $\text{pH} < 7,10$  var 0,6 vid 37 veckor och ökade kontinuerligt till 1,5 vid 42 veckor, men med gestationsåldersrelaterade normalvärden förelåg ingen ökning av OR vecka 37-41 och ökade inte signifikant förrän vecka 42+. Gestationsåldersrelaterade normalvärden bör således användas för att minska risken för en falsk acidosisdiagnos vid födelsen.

## **STRESZCZENIE W JĘZYKU POLSKIM**

W Szwecji rejestruje się 98 % wszystkich ciąż podczas badania ultrasonograficznego na początku drugiego trymestru i wtedy też ustala się dzień, w którym ciąża będzie donoszona, to znaczy datę spodziewanego rozwiązania. Upłynie wtedy 40 pełnych tygodni, oznaczonych jako 40 pełnych tygodni i 0 dni (40 + 0), odpowiadające 280 dniom. Innym określeniem jest powiedzenie, że ciąża jest w terminie. Jeśli kobieta nie urodzi dwa tygodnie po wyliczonym terminie (42+0, 294 dni) określa się ciążę jako przenoszoną. Zaletą obliczania długości ciąży przez badanie USG, a nie liczenie jej od ostatniej menstruacji jest to, że obliczenie takie jest dokładniejsze, z odsetkiem przenoszenia 4-7 % zamiast 9-10 %.

Od dawna znane jest, że krzywe perinatalnej śmiertelności i zachorowalności obydwie wskazują przebieg formatu U, z najniższym punktem w 40 tygodniu i wzrostem wraz z oddalaniem się od tego punktu w obydwu kierunkach. Przenoszenie ciąży oznaczają zwiększone ryzyko w porównaniu z rozwiązaniem w terminie. Nadto komplikacją w przypadku przenoszenia, poza zwiększoną śmiertelnością, jest między innymi zwiększone ryzyko zespołu aspiracji smółki z ciężkimi zaburzeniami oddychania jako następstwem, uszkodzenia okołoporodowe ze względu na zwiększone rozmiary dziecka, jak również tężyczka w okresie noworodkowym.

Poprzez opiekę w okresie ciąży i porodu czyni się ogromne starania w celu zmniejszenia ryzyka komplikacji w przypadku przenoszenia ciąży. W odróżnieniu od porodu przedwczesnego, gdzie kobieta często przybywa na oddział porodowy z trwającymi już bólami, to w przypadku przenoszenia jest możliwe - z medycznego punktu widzenia - zmniejszenie ryzyka komplikacji. Celem jest wówczas rozpoznanie przypadków ryzyka i efektywne spowodowanie rozwiązania, natomiast kobiety bez komplikacji mogą kontynuować swoją ciążę pod zintensyfikowaną kontrolą i nadzorem lekarskim. Zagranicą jest powszechne, że po prostu indukuje się poród u wszystkich pacjentek, których ciąża przekroczyła 41 tydzień lub jeszcze wcześniej. W Szwecji stosowana jest ogólnie powszechna linia zachowawcza, ponieważ pozwala się wtedy na spontaniczne rozpoczęcie porodu i tym samym zmniejsza ryzyko komplikacji wyłącznie z tego powodu, że indukuje się poród.

Przenoszenie ciąży jest w kontekście położniczym problemem stosunkowo późno zauważonym i dlatego spora część postępowania klinicznego jest kontrowersyjna lub niejasna. W niniejszej pracy naświetla się niektóre klinicznie ważne aspekty przenoszenia ciąży: (1) znaczenie w przenoszonym czasie źle i zbyt długo obliczonej długości ciąży w przypadku płodów męskich i źle, zbyt krótko obliczonej w przypadku płodów żeńskich, w związku z tym, że nie wzięto względu na płeć płodu podczas badania ultrasonograficznego w drugim trymestrze; (2) znaczenie wcześniej zastosowanego zintensyfikowanego nadzoru nad płodem w przypadku przenoszenia; (3) potencjalną korzyść zastosowania przepływu mózgowego krwi i diagnostyki przepływu oszczędzającego mózg (brain-sparing), jako narzędzie nadzoru w przypadku przenoszenia; i (4) fizjologiczny rozwój kwasicy u płodu ze zwiększającą się długością ciąży i jej znaczenie, gdy wartość pH w krwi pępowinowej używa się jako oceny stanu perinatalnego.

Prace te bazuje głównie na danych zaczerpniętych z rejestru bazy danych w Klinice Położniczej w Malmö (MacOB), południowo-szwedzkim okręgu opieki zdrowotnej (Perinatal Revision Syd), Medycznego Rejestru Urodzin, Rejestru Zgonów i Rejestru Pacjentów. Wiele danych z MacOB i Perinatal Revision Syd zastosowano w celach badawczych.

**Pierwsza część pracy** ocenia o kliniczne konsekwencje faktu, że wszystkie płody określa się jako równej wielkości w trakcie badania ultrasonograficznego w drugim trymestrze. Wcześniej uważano, że różnica między płodami męskimi i żeńskimi, odpowiadająca 1,5 dnia długości ciąży nie ma klinicznego znaczenia w materiale szwedzkim. W materiale obejmującym 82484 donoszonych dzieci urodzonych w jedenastu szpitalach południowej Szwecji znaleźliśmy OR (odds ratio) w wysokości 1,41 dla chłopców w przypadku przenoszenia. Fakt, że chłopcy są częściej przenoszeni znane było już wcześniej i kliniczne znaczenie tego faktu jest wątpliwe - być może powinno się odczekać z rutynowym indukowaniem porodu w przypadku płodów męskich. W odniesieniu do dziewczynek ryzyko niskiej skali Apgar w chwili narodzin było większe niż u chłopców, ale nie było znamienności statystycznej ( $P=0,087$ ).

**W drugiej części pracy** oceniliśmy, w jakim stopniu wczesne ustalenie „kontroli przenoszonych ciąż” mogłoby zmniejszyć zachorowalność i śmiertelność. Już prawie od dwóch dziesięcioleci przenoszenie ciąży kontrolowane są w Malmö w sposób prawie niezmienny. Prześledziliśmy zintensyfikowany nadzór z oceną

kliniczną, ultradźwiękami dot. kontroli przyrostu, pomiarem objętości wód płodowych, kardiokografią (CTG) i przepływem krwi w pępowinie wykonanym dokładnie w 42 tygodniu (42+0), to znaczy w dniu, w którym zaczyna się definiować przenoszenie. Wcześniejsze kontrolowanie mogłoby spowodować zwiększone obciążenie pracą, zaś późniejsze zwiększone ryzyko dla dziecka. Pracownie USG i laboratoria krwi są zamknięte w weekendy i dni świąteczne, a kobiety z przenoszoną ciążą skontrolowano w poprzedzający piątek, tzn. w 41 tygodniu + 6 dni lub 41 tygodniu + 5 dni. W niektórych wypadkach kontrole miały miejsce w tygodniu 41+4 lub 42+1. Ponieważ odnotowaliśmy bardzo dokładnie w bazie danych, w którym dniu ciąży odbyło się badanie USG i kontrola przepływu krwi, możemy teraz w quasi-randomizowany sposób ocenić różnicę wyniku, jeśli kontrola przeprowadzona została w tygodniu 41+4-5, 41+6 lub 42+0. 2032 przypadków skontrolowano w ten sposób w okresie 1990-2005. Dostrzegliśmy, że wcześniejsze kontrolowanie nie zmieniło końcowego wyniku, to może zależeć od tego, iż poradnie dla kobiet są dość efektywne w znajdowaniu komplikacji, tak że cięższe, które przechodzą w cięższe przenoszone są częściej niż przeciętnie nieskomplikowane. Wykonaliśmy dlatego porównanie z grupą kontrolną 11784 kobiet z ciążą bez komplikacji z rozwiązaniem w tygodniu 40+0  $\pm$ 3 dni. Porównanie wykonano z danymi z Rejestru Pacjentów i Rejestru Zgonów. Dostrzegliśmy, jak się spodziewaliśmy, że śmiertelność okołoporodowa w grupie ciężych przenoszonych była wyższa, ale niespodziewanie okazało się również, że zachorowalność w wieku dziecięcym była niższa.

**W trzeciej części pracy** oceniono, jaką korzyść można osiągnąć poprzez rutynowe przeprowadzanie pomiarów przepływu krwi w środkowej tętnicy mózgu w przypadkach przenoszenia ciąży. W latach 1992-1996, 229 kobiet z przenoszoną ciążą przeszło rutynowe badania uzupełnione badaniem przepływu krwi w środkowej tętnicy mózgu. Wyniki wcześniejszego badania nie zostały przekazane do klinik. Niewydolność łożyska jest spodziewaną komplikacją w przypadku przenoszenia a może ono z kolei powodować zły przyrost płodu i/lub niedotlenienie płodu, co z kolei powoduje że płód kompensuje niedobory tlenowe poprzez centralizację krążenia do organów życiowo ważnych takich jak: mózg, serce i nadnercza. Redystrybucja przepływu krwi do mózgu nazywa się brain-sparing i oznacza, że opór przepływu naczyniowego krwi zmniejsza się. Ultradźwiękową metodą Dopplera można łatwo oznaczyć opór przepływu w środkowej tętnicy mózgu. Wychodząc z rutynowego programu badawczego zawierającego kardiokografię, ultradźwięki, objętość wód płodowych, przepływ

krwi w tętnicy pępowinowej, pomiar ciśnienia krwi, paskowe badanie moczu itd. zidentyfikowaliśmy i oznaczyliśmy, w jakim stopniu brain-sparing, przede wszystkim w grupie prowadzonej zachowawczo, mógłby się przyczynić do zapobiegnięcia lub złagodzenia komplikacji u dziecka. Odkryliśmy, że pomiar przepływu krwi mózgowej nie wniósł jakiegóż szczególnej poprawy, ale z drugiej zaś strony nie było żadnych chorych, bądź dotkniętych komplikacjami dzieci wśród tych, które miały brain-sparing jako płód (17 przypadków, 7 %). Kontynuacja i nawiązanie z danymi z Rejestru Pacjentów nie wykazały różnicy w zachorowalności w wieku dziecięcym między dziećmi, które miały, a tymi, które nie miały objawu przepływu oszczędzającego mózg (brain-sparing) w okresie płodowym.

**Czwarta część pracy** dotyczy wartości pH w tętniczej krwi pępowiny jako położniczego parametru jakościowego. Gazy w krwi pępowiny używane są (A) klinicznie w celu oceny przebiegu rozwiązania w indywidualnych przypadkach, (B) jako położniczy parametr jakościowy, i (C) jako wypadkowy parametr w badaniach klinicznych. Tradycyjnie używa się  $\text{pH} < 7,10$  jako wskaźnik kwasicy, ale ponieważ pH spada wraz z długością ciąży taka graniczna wartość daje zafałszowany obraz zachorowalności. Wartość pH w tętniczej krwi pępowiny określono w 24390 nagle urodzonych dzieci w tygodniach ciąży 37-42+. Wartość pH spada liniowo wraz z długością ciąży. Odds ratio (OR) wartości  $\text{pH} < 7,10$  wynosiło 0,6 w 37 tygodniu i rosło w sposób ciągły do 1,5 w tygodniu 42, ale z wiekiem płodowym normalnymi wartościami nie zachodził wzrost wartości OR w tygodniach 37-41 i nie wrosła istotnie przed tygodniem 42+. Wartości odpowiadające wieku płodu, winny być zatem używane w celu zmniejszenia ryzyka błędnej diagnozy kwasicy w chwili urodzin.

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