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SHORT-TERM NEONATAL OUTCOMES FOLLOWING VARIOUS MODES OF DELIVERY

Ph.D. Thesis

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LIST OF PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Gyurkovits Z, Kálló K, Bakki J, Katona M, Bitó T, Pál A, Orvos H. Neonatal outcome of macrosomic infants: an analysis of a two-year period. Eur J Obstet Gynecol Reprod Biol 2011;159:289-292. (IF: 1.974)

II. Gyurkovits Z, Hracskó Zs, Zimányi M, Varga Sz.I, Németh G, Pál A, Orvos H. Comparison of oxidative stress markers in vaginal deliveries with or without epidural analgesia. Redox Rep 2013;18(1):8-11. (IF: 1.732)

III. Gyurkovits Z, Kálló K, Bakki J, Katona M, Németh G, Pál A, Orvos H. Négyezer gramm és afeletti születési súllyal világra jött újszülöttek neonatológiai adatainak elemzése. Magy Nőorv Lapja 2013;76(1):26-30. (IF:-)

Lectures on the topic of the Ph.D. thesis

Gyurkovits Z, Bakki J, Katona M, Bitó T, Pál A, Orvos H. Macrosomic infants in our neonatal department – is it a macro dilemma? XXXII. Alpe-Adria Meeting of Perinatal Medicine Italy, Bassano del Grappa, 2010

Gyurkovits Z, Kálló K, Bakki J, Katona M, Németh G, Pál A, Orvos H. Neonatal outcome of macrosomic infants. XXIII European Congress of Perinatal Medicine, Paris, 2012

Gyurkovits Z, Szabó H, Radics B., Maár B, Orvos H, Hantos Z. Noninvasive measurement of respiratory mechanics in healthy newborns. XXXIV Alpe-Adria Meeting of Perinatal Medicine, Szeged, 2012

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Radics B, Gyurkovits Z, Szabó H, Maár B, Orvos H, Sly P, Hantos Z. Within-breath changes in respiratory impedance in healthy neonate. European Respiratory Society Annual Congress, Vienna, 2012

ABBREVIATIONS

BE: base excess
BW: birth weight
CAT: catalase
CS: caesarean section
EA: epidural analgesia
ECS: elective caesarean section
Ers: respiratory system elastance
ENaC: epithelial Na^+ channel
FOT: forced oscillation technique
*f*res: resonant frequency of the respiratory system
GA: gestational age
GDM: gestational diabetes mellitus
GPs: glutathione peroxidases
GSH: glutathione
IC_{50}: half-maximum inhibitory concentration
IUGR: intrauterine growth retardation
Irs: respiratory system inertance
LP: lipid peroxidation
NICU: neonatal intensive care unit
OECD: Organisation for Economic Co-operation and Development
OGTT: oral glucose tolerance test
P: pressure
RBC: red blood cell
RDS: respiratory distress syndrome
ROS: reactive oxygen species
Rrs: respiratory system resistance
SD: standard deviation
SODs: superoxide dismutases
SVD: spontaneous vaginal delivery
TBA: thiobarbituric acid
TTN: transient tachypnoea of the newborn
V': flow
WHO: World Health Organization
Xrs: respiratory system reactance
Zrs: respiratory system impedance

1. INTRODUCTION

1.1. Changes in the rates of caesarean section

Caesarean section (CS) was introduced in clinical practice as a lifesaving procedure both for the mother and for the baby. Surprisingly, the rate of CS increased strikingly and disproportionately in some parts of the world between 1970 and 2009; for instance, the overall rate of CS rose from 6.1% to 31.9% in Hungary, and a similar tendency was seen in the U.S.A., with a rise from 5.5% to 31.8% [1]. In 1985 the World Health Organization (WHO) stated: "There is no justification for any region to have CS rates higher than 10-15%" [2], nevertheless, the optimum rate of births by CS two decades later remains a matter of controversy in both developing and developed countries.

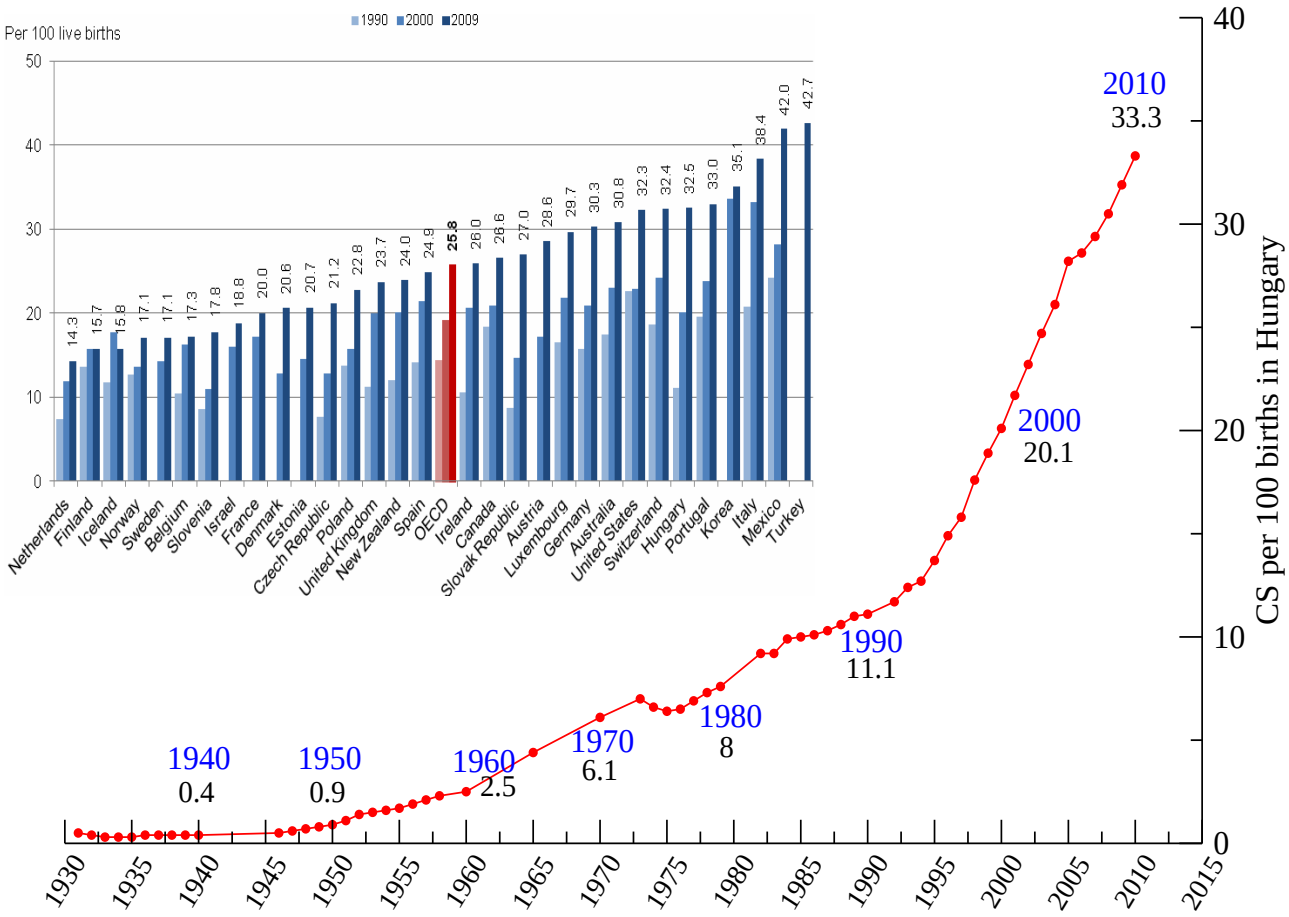

Figure 1. Rate of CS per 100 live births in Hungary since 1930. (Inset: Rate of CS per 100 live births between 1990 and 2009. With copyright permission; source: OECD Health Service 2011.)

In developing countries, the lack of availability of or access to maternal health services and the underuse of CS are some of the many factors predisposing to high maternal and perinatal mortality. The WHO data indicate that those undeveloped nations with the lowest CS rates have staggeringly high maternal mortality, with more than 1 in 100 labours resulting in the mother's death, with an accompanying high rate of neonatal mortality.

On the other hand, maternal mortality in much of Europe and North America is in the range 0.001-0.03% and the neonatal mortality rate is under 0.5% [3]. Among others, this is due to the improved level of prenatal and hospital care during delivery, the more frequent use of CS, the introduction of antenatal steroid therapy, the development of high-standard neonatal intensive care units (NICUs) with sophisticated mechanical ventilation, the administration of surfactant therapy and the new methodolgies in maternal anaesthesia and analgesia. In these countries, modern obstetric technology makes it possible for women to maintain higher-risk pregnancies than ever before. Furthermore, women who are infertile or past their peak of fertility can receive reproductive assistance and become pregnant. Women of advanced maternal age and those who receive fertility treatments of certain types have an increased probability of giving birth to twins, who are usually delivered by CS. In some of the developed countries, therefore, attention has focused more on strategies to reduce the unjustifiable high CS rate as it does not confer an additional health gain, but may increase the risks, with implications for future pregnancies and health services.

After all, it is evident that the balance of benefits and burdens associated with the performance of CS has changed dramatically during the past century. With the advent of highly effective antibiotics, improved operative techniques, blood banking and advances in anaesthesia, the reticence to perform CS was greatly reduced. Meanwhile, data accumulated in the literature that pointed out the risks of spontaneous vaginal delivery (SVD) for various groups of women (e.g. those with a prior uterine scar, an uninducible cervix and breech infants). The lawsuits relating to failure to perform a timely CS in prolonged labour and delivery also moved its rate upward. Furthermore, the level of comfort of obstetricians with somewhat difficult deliveries (e.g. assisted breech delivery) declined as their experience with those deliveries diminished. In essence, the era of the heroic vaginal delivery had come to an end.

The pregnant woman is also usually more willing to accept a substantial risk to herself to decrease the risks to her newborn child. This observation points to the problem of CS at

maternal request without a medical and obstetrical indication, which is a current trend in the U.S.A. There are markedly different practice recommendations worldwide regarding CS, and especially those at maternal request. The American College of Obstetricians and Gynecologists states that [4]: "In the absence of significant data on the risks and benefits of cesarean delivery…,if the physician believes that cesarean delivery promotes the overall health and welfare of the woman and her fetus more than vaginal birth, he or she is ethically justified in performing a cesarean delivery." In contrast, the International Federation of Gynecology and Obstetrics states that [5]: "At present, because hard evidence of net benefit does not exist, performing cesarean delivery for nonmedical reasons is not ethically justified." The Hungarian Society of Obstetrics and Gynaecology does not justify CS at maternal request; it recommends action in accordance with the absolute or relative indications. The obligatory criteria include cardiac diseases, pulmonary oedema, disseminated intravascular coagulation, acute bleeding, fetal asphyxia, umbilical prolapse, eclampsy, placental abruption or rupture of the uterus [6].

A number of risks influence the forms and rates of neonatal morbidities of different delivery modes. Respiratory morbidity was earlier found to be substantially more common among infants delivered by elective CS (ECS), whereas intracranial haemorrhage, brachial plexus injury and culture-positive sepsis were less common [7]. An increase in respiratory morbidity (either respiratory distress syndrome (RDS) or transient tachypnoea of the newborn (TTN)) among neonates born by CS has been widely reported in the literature, starting in the 1960s [8]. The pathomechanisms proposed for this association include iatrogenic prematurity [9] and an attenuation of the catecholamine surge during labour [10]. Performing ECS only after a gestational age (GA) of 39 completed weeks has been shown to cause a sharp reduction in the risk of iatrogenic prematurity and RDS [10], and ECS performed after the onset of labour decreases the risk of respiratory morbidity further. Still, vaginal delivery remains the mode of delivery associated with the lowest risk of neonatal respiratory distress.

The rate of CS is also significantly greater in some high-risk groups, e.g. in preterms, in intrauterine growth retardation (IUGR) or in macrosomia. In the first part of our study, we focused on macrosomic neonates. Secondly, we investigated the possible modification of epidural analgesia (EA) in the process of oxidative stress in neonates born by SVD, as in cases of SVDs, the attenuation of labour pain by EA is one of the well-known procedures

used worldwide. Finally, in the third part, we established a neonatal lung function test with which we compared lung mechanical parameters in SVD versus CS cases.

1.2. Macrosomia

To perform CS in the case of a macrosomic fetus is a dilemma. There is no general consensus as concerns the definition of the term fetal macrosomia. The classical definition for a large-for-gestational-age neonate is a birth weight (BW) more than or equal to the 90th percentile for a given GA. Alternatively, the term macrosomia can be utilized for neonates with a BW greater than 4000, 4500 or 5000 g, irrespective of the GA as an absolute limit [12]. However, the American College of Obstetricians and Gynecologists suggests a threshold of 4500 g, as the morbidity increases sharply beyond this [13]. The prevalence of macrosomia has been increasing in recent decades, with an accompanying elevated risk of an adverse outcome for mother, fetus and neonate. It is well known that there are differences in neonatal anthropometric data across geographical populations; for instance, the incidence of macrosomia varies between 5% and 20% [14].

The cause of fetal macrosomia still cannot be determined exactly, since it seems to involve several factors, including environmental, genetic, maternal and fetal features [15]. Among the factors which influence fetal macrosomia are primarily the genes which control cell growth and differentiation, and hormones such as insulin, insulin-like growth factors, thyroxine, leptin and their receptors. With the upcoming concept of epigenetic regulation, it has become evident that nutritional and other environmental factors during fetal life may modify the long-term expression of genes. Pedersen [16] hypothesized that maternal hyperglycaemia stimulates fetal hyperinsulinaemia, which mediates growth. The risk factors include maternal diabetes mellitus (both pre-gestational and gestational (GDM)), impaired glucose tolerance, prolonged gestation (>41 weeks), maternal obesity, a pregnancy weight gain >20 kg, maternal height, multiparity, male fetal sex, white maternal race and a previous large infant [17]. Modifiable hazard factors include life-style-related issues of the mother: an increased maternal nutritional intake and a low level of physical activity. Smoking reduces BW, but, in general, non-smoking mothers have healthier neonates than do smoking mothers [18]. Fetal diseases, such as erythroblastosis fetalis, nesidioblastosis, tumours and numerous syndromes [19] can result in heavy babies.

Fetal overgrowth has both short- and long-term perspectives for both the mother and the neonate. The short-term maternal risks include prolonged labour, perineal lacerations, uterine atonia, abnormal haemorrhage and CS [20], while the short-term neonatal risks are shoulder dystocia, hypoxia, plexus injuries, hypoglycaemia and a need for intensive care [21]. Among the long-term risks for the mother, type 2 diabetes mellitus, cardiovascular disease and obesity [22], and for the neonate cancer have to be mentioned [23].

1.3. Oxidative stress

The Romans referred to delivery as the poena magna, i.e. the “great pain” or “great punishment”. On the other hand, labour in primitive cultures is regarded as a natural process not considered painful by women, which should be handled with preparation rather than some form of pain medication. The mechanism by which people perceive different levels of pain from the same stimulus remains unclear. The maternal labour pain is not believed to have a direct effect on the fetus, but indirectly it can affect a number of systems in consequence of the release of epinephrine, norepinephrine, oxytocin and other bioactive agents.

Physicians have debated the safety of obstetric anaesthesia since 1847, when James Young Simpson first administered anaesthesia for delivery, using diethyl ether. Simpson’s innovation evoked strong criticism from contemporary obstetricians, who questioned its safety and its wisdom. The most persistent critic was Charles D. Meigs; the basic contrast between them was their interpretation of the nature of labour and the significance of labour pain. Simpson held the view that labour pain is without physiological value and only degrades those who experience it. In contrast, Meigs argued that labour pain has a purpose, and any drug that abolishes pain will alter contractions; physicians should therefore not intervene with potentially disruptive drugs. Despite such controversy, physicians quickly incorporated anaesthesia into clinical practice, largely because of their patients’ desire to avoid childbirth pain. Important milestones in obstetric anaesthesia were the expanded use of opioids in the early decades of the twentieth century and the refinement of regional anaesthesia starting in the mid-twentieth century. Outstanding conceptual developments included the idea of Zweifel that a drug given to the mother may cross the placenta and affect the fetus, while Apgar considered that the condition of the newborn is the most sensitive assay of the quality of anaesthetic care of the mother.

EA is nowadays a widely-accepted, safe and reliable method of labour pain relief. It has proved to be beneficial to both mother and child, and improves the levels of placental perfusion and oxygenation of the fetus. However, it can be associated with a longer second stage of labour, more frequent oxytocin augmentation, hypotension and fever, due to changes in the maternal inflammatory reactions, and this may possibly affect the neonatal outcome as well [24].

The normal neonatal physiological responses to the birth process are complex. In particular, shortly after birth, newborns must adapt to abrupt changes in O_2 concentration and to the increased generation of reactive oxygen species (ROS) after their entry into the normoxic environment. The process of birth involves an enhanced degree of oxidative stress for the infant. It is debated whether this stress is a necessary event in the feto-neonatal transition. In 1988, Saugstad conjectured that there may be a link between extreme oxidative stress and neonatal morbidity [25]. Since then, several studies have suggested a connection between oxidative stress and various neonatal disorders [26]. A recent microarray analysis indicated that healthy term fetuses prepare for their impending transition with highly expressed levels of several antioxidant enzymes and associated pathways [27].

For the efficient production of energy, molecular oxygen (O_2) is required as an electron acceptor in all living aerobic organisms. The cell-damaging effects of highly reactive oxygen species such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), etc. are exerted via a variety of physiological and pathophysiological reactions and have been implicated in many diseases and the process of ageing. Most living organisms have developed well-integrated antioxidant defences to scavenge free radicals. These mechanisms include enzymes, e.g. superoxide dismutases (SODs), catalase (CAT) and glutathione peroxidases (GPs), and other molecules, e.g. glutathione (GSH), vitamins C and E and beta-carotene. Oxidative stress may arise when the balance between ROS and antioxidants is disturbed. The ROS can cause intracellular oxidative damage to proteins, nucleic acids and lipid membranes through the peroxidation of unsaturated fatty acids. The ROS serve as important cell signalling molecules, but in excess they can contribute to the pathophysiology of various diseases associated with a low antioxidant capacity (such as retinopathy and bronchopulmonary dysplasia) [28].

The effects of different delivery modes on the oxidative balance have already been investigated in numerous articles [29]. The literature seems to agree on the fact that local anaesthetics also have a potential antioxidant effect [30].

1.4. Lung function techniques

One of the greatest challenges facing a newborn after birth is the task of making a smooth transition to air breathing. For the effective gas exchange to occur, the alveolar spaces must be cleared of excess fluid and the pulmonary blood flow increases to match ventilation with perfusion. Failure of either of these events can harm the neonatal transition and cause the infant to develop respiratory distress. It is clear that besides Starling forces and the vaginal squeeze, the amyloride-sensitive Na^+ transport by the lung epithelia through epithelial Na^+ channels (ENaCs) is the key event in the transepithelial movement of alveolar fluid. The active Na^+ transport across the pulmonary epithelium drives liquid from the lung lumen to the interstitium, with subsequent absorption into the vasculature. Gowen and co-workers were the first to show that the immaturity of Na^+ transport mechanisms contributes to the development of the TTN [31]. Several factors have been proposed to have lung-specific effects on Na^+ reabsorption, including glucocorticoids, O_2, ß-adrenergics and surfactants [33]. There is considerable evidence that high levels of endogenous catecholamines at birth may be important for accelerating alveolar fluid clearance by increasing the activity of the fetal Na^+ channel.

A low lung function at birth is known to be a significant risk factor for acute and chronic lung disease throughout life. It is increasingly recognized that adult diseases have their origin in childhood and this is true for respiratory diseases too. The Tucson Children Respiratory Study was the first longitudinal assessment of the natural history of asthma that included infant lung function tests [34] and also the first to provide evidence that a diminished airway function precedes wheezing illness. Similar findings were reported from the Boston study [35] and the London study, which found elevated premorbid values of airway resistance in those who subsequently wheezed in the first year [36,37]. Lung growth is determined by genetic factors and is susceptible to a variety of pre- and postnatal insults and environmental exposures. It has been shown that preterm delivery, even in the absence of any neonatal respiratory disease or ventilator support, may have an adverse effect on subsequent lung growth and development, which persists and may even worsen throughout the first few years of life [38]. Lower respiratory tract illnesses are a major cause of morbidity in infancy, and therefore are of considerable importance.

Several infant lung function techniques have been developed over the last 30 years with considerable methodological progress and refinement, but most require sophisticated equipment and sedation, and the reference values for the variables are scarce. The major role for lung function testing in infants still remains mainly within the research area. It has been extensively used to examine the underlying pathophysiology and response to therapeutic interventions in a variety of respiratory diseases during early life. The most commonly used test in paediatric pulmonology is the one with forced expiration, but other individual techniques, such as occlusion techniques, the interrupter technique, oesophageal manometry, whole-body plethysmography, respiratory inductive plethysmography or measurements of lung volume by inert gas dilution, can play roles in special circumstances. Application of these tests in clinical research studies has furthered our knowledge with respect to the early determinants of the airway function, including the adverse effects of preterm delivery, IUGR and pre- and postnatal exposure to tobacco smoke. Furthermore, lung growth and development following neonatal lung diseases can now be better understood. Lung function tests have also been used as objective outcome measures to assess the effects of different types of ventilatory support, including extracorporeal membrane oxygenation and high-frequency oscillation [39, 40].

There is increasing awareness that airway resistance and forced expiratory flows are determined not only by the calibre of the airways, but also by the compliance of the airway wall and the recoil of the surrounding parenchyma, leading to a search for suitable parameters that will reflect these characteristics.

The forced oscillation technique (FOT) was developed in 1956 by DuBois et al. [41], who described the application of a series of sinusoidal pressure waves of varying frequencies to the airway opening or the body surface. The development of the FOT has expanded exponentially in recent years to the point that commercial equipment based on standardized approaches is now available. In contrast with spirometry, which requires high level of subject effort, the FOT requires no more than quiet tidal breathing for short periods of time. This requirement makes it an ideal lung function test for use in young children in whom active cooperation is difficult to achieve. The underlying principle of the FOT is the application of an external signal, small-amplitude pressure oscillations on the respiratory system and measurement of the resultant oscillatory flow. This response is termed the respiratory system impedance (Zrs), and is the frequency-dependent relationship between pressure (P) and flow

(V’). Impedance is a generalization of resistance, but whereas resistance describes only resistive induced pressure differences, impedance describes pressure differences across resistive, elastic or inertive elements. Zrs can be divided into its real (resistive, Rrs) and imaginary (reactive, Xrs) components. Resistance describes the dissipative properties of the respiratory system, whereas reactance is related to the energy storage capacity and thus is determined jointly by the elastic and inertial parameters.

The advantages of the FOT are that it provides a non-invasive way to evaluate the respiratory system, and the ability to apply either a single frequency or a band of frequencies which provide useful information about the respiratory structures. The FOT has proved to be helpful in assessing bronchoactive responses, in titrating the optimum positive end-expiratory pressure, and in the follow-up of changes in respiratory mechanics during conventional mechanical and non-invasive ventilation. The FOT combined with functional residual capacity measurements can detect abnormalities in the symptom-free intervals of wheezing infants.

These qualities of the FOT make it an ideal tool with which to study airway patency during the neonatal period, and to detect the possible differences in lung mechanics between neonates born by SVD and those born by CS.

2. AIMS OF THE STUDY

The specific objectives of the study were:

- to compare the neonatal outcomes and modes of delivery in macrosomic and normal BW groups and to analyse the macrosomic subgroups (4000–4499 g, and ≥4500 g) in detail in order to explore a possible correlation between morbidities, BW and the mode of delivery;

- to determine and compare fetal oxidative stress indices, levels and activities of antioxidants in the cord blood of singleton, full-term neonates of mothers who received EA on request versus normal SVDs without administration of pain control, and to assess the neonatal outcomes;

- to establish Zrs data with the FOT superimposed on spontaneous breathing in full-term non-sedated newborns born by CS versus those born by SVD, and to compare the impedance spectra of newborns born by CS or by SVD with postnatal maturation in the 3 subsequent days of life.

3. MATERIALS AND METHODS

3.1. Studies on macrosomic infants

This was a retrospective study on singleton pregnancies of women who delivered between 01.01.2008 and 31.12.2009 at the Department of Obstetrics and Gynaecology, University of Szeged, Hungary. The inclusion criteria were a GA at delivery of at least 37 completed weeks and a BW of at least 2500 g. There were two main groups: the first group comprised neonates with BW 2500-3999 g; this was the control group. The second group comprised the neonates weighing at least 4000 g. These neonates were further stratified into two subgroups from the aspect of their BW (4000-4499 g, and ≥4500 g) and the diabetic history of the mother.

The neonatal outcome was investigated with regard to the following features: the umbilical cord blood pH, the 5-min Apgar score, fracture of the clavicle, cephalhaematoma, adrenal haemorrhage, neurological disorders, congenital anomalies, hypoglycaemia, hyperbilirubinaemia, respiratory disorders, admission to a NICU, mechanical ventilation and perinatal mortality.

The definition of hypoglycaemia was a blood glucose level <2.6 mmol/l. Blood glucose was checked at 1, 3, 6, 24 and 72 hours of age, or more frequently in the event of hypoglycaemia.

Screening for GDM was performed with the WHO-recommended 75-g oral glucose tolerance test (OGTT) at a GA of 24 to 28 weeks. The diagnosis of GDM was made when the fasting and 2-hour glucose values were sufficient for a diagnosis of either impaired glucose tolerance or GDM. Those pregnant with risk factors for GDM underwent the screening in early pregnancy, and in the event of a negative OGTT, a repeated test was done at a GA of 24-28 weeks. Hyperbilirubinaemia was defined according to the Clinical Practice Guideline of the American Academy of Pediatrics published in 2004 [42]. Adrenal haemorrhage was diagnosed by ultrasonography, as part of the existing routine abdominal ultrasonographic screening programme at the Department of Obstetrics and Gynaecology, University of Szeged.

Statistical analysis was performed by using the chi-square test; a level $p<0.05$ was considered to be statistically significant.

3.2. Comparison of oxidative stress markers in vaginal deliveries with or without epidural analgesia

This prospective study, approved by the Ethics Committee at the University of Szeged, involved a total of 86 singleton infants born by SVD and their healthy, non-smoking mothers. The parturients were of matched mixed parity in active, spontaneous term labour after an uncomplicated pregnancy. The mothers received full pregnancy care.

The exclusion criteria included the use of any medication, coexisting diseases, instrumental delivery or CS. The cord blood samples were provided by the Department of Obstetrics and Gynaecology, Medical University of Szeged, Hungary. Eighty-six singleton full-term mature neonates of either sex, born at a GA between 37 and 41 weeks, were selected, 36 in the EA group, and 50 in the control group.

At enrolment, the level of cervical dilation was 3-6 cm. The participants in the study group received EA on request (EA group, n=36), whereas the mothers in the control group did not desire any pain relief (control group, n=50), except for 1% lidocaine before episiotomy.

In the EA group, with the patient in a sitting position, an epidural catheter was inserted, usually to the L3-L4 interspace, using a midline approach with the loss-of-resistance technique. Following a test dose of 3 ml of 2% lidocaine, a bolus dose of 2-3 ml of 0.1-0.2% ropivacaine was administered, followed by a continuous infusion of 20 ml of 0.1% ropivacaine with 0.1 mg of fentanyl at a rate of 4-8 ml per hour during labour. If necessary, a repeated course was given at the patient’s request. The basic haemodynamic parameters, body temperature and cardiotocographic parameters were monitored.

Immediately after delivery, a segment of the umbilical cord was double-clamped, and blood was drawn from the artery into preheparinized plastic syringes in both groups. Coagulation was inhibited with EDTA. The whole-blood samples were analysed within 5 min of collection for pH and base excess (BE). Acidaemia was defined as an umbilical arterial blood pH<7.2 or/and umbilical arterial BE <-12 mmol/l (a BE of -12 mmol/l is approximately 2 SDs below the mean). Maternal acidaemia as a cause of cord blood acidaemia was excluded. For the oxidative stress markers, the duration of storage was kept as short as possible, without adding any preservative, with a maximum of 1 week. The blood samples were centrifuged at 1500 rpm for 10 min and the plasma and the buffy coat were removed. The red blood cells (RBCs) were haemolysed after repeated washing with isotonic saline at

pH 7.0 by the addition of distilled water in a ratio of 1:9 and were kept at -20 ^{o}C until processing. With the exception of the SOD activity determinations, the aliquots of the haemolysates were used directly.

Total protein determination: The quantity of proteins was determined with the Folin reagent, bovine serum albumin being used as standard [43].

Determination of GSH level: The GSH level of the RBCs was determined with Ellman's reagent [44]. Proteins were precipitated with 5% trichloroacetic acid in order to eliminate protein-linked -SH groups from the measurements.

SOD assay: Before the determination of SOD activity, the haemolysates were treated with ethanol:chloroform (2:1) to remove haemoglobin from the samples, and then centrifuged. The supernatants were used for SOD activity determinations via inhibition of the epinephrine-adrenochrome transformation [45].

The enzyme activities were calculated from the widely applied (for an enzyme, cell or microorganism) half-maximum inhibitory concentration (IC_{50}) method.

CAT assay: For the CAT assays, RBC haemolysates (100-fold dilution) were used. CAT activity was measured via the H_2O_2 degradation spectrophotometrically at 240 nm. The results were expressed in Bergmeyer units. One BU is the amount of CAT that decomposes 1000 mg H_2O_2/min [46].

GP assay: With cumene hydroperoxide and GSH as substrates, GP was determined spectrophotometrically at 412 nm [47].

Lipid peroxidation (LP) assay: The LP of the RBCs was determined by the thiobarbituric acid (TBA) method, which reveals the level of total TBA-reactive substances. Calibration was performed with malonyldialdehyde [48].

Spectrophotometric measurements were made with a Thermo Spectronic Biomate 5 instrument.

Statistical analysis of the data was performed with Student's t-test. A level of $p<0.05$ was accepted as indicating statistical significance. The Shapiro-Wilks test was applied to confirm the normality of the values. The reported values are means ± SD.

3.3. Neonatal lung function tests

Study population

In this prospective study, approved by the Ethics Committee of the University of Szeged, 42 full-term, healthy singleton newborns were recruited at the Department of Obstetrics and Gynaecology, University of Szeged, Hungary, after written informed parental consent had been obtained. The exclusion criteria included any congenital abnormalities, coexisting diseases or the use of any medication. The neonates were divided into two groups: 19 were born by SVD (BW: 3.15 ± 0.42 kg), and 23 by CS (BW: 3.28 ± 0.47 kg). They were studied on the 1st, 2nd and 3rd days of life. The measurements were made by the FOT during quiet sleep at least 30 min after a feed. Oxygen saturation and heart rate were monitored continuously throughout the study.

Measurement of oscillatory mechanics

For the measurement of Zrs, low-amplitude (<2 hPa) pseudorandom forced oscillations in the 8-to-48-Hz frequency range were superimposed on the spontaneous breathing. Pseudorandom noise is a periodic signal designed specifically to include only a designated set of desired frequency components, each represented by a precisely defined amplitude.

The instrument employed for the estimation of Zrs included a wave tube connecting the source of forced oscillations, i.e. the loudspeaker, and the subject. Zrs is measured as the load impedance on the wave tube, on the basis of the geometric and physical properties of the tube and the inside air, and the pressure recorded at the inlet (P_1) and outlet of the tube (P_2).

Set-up

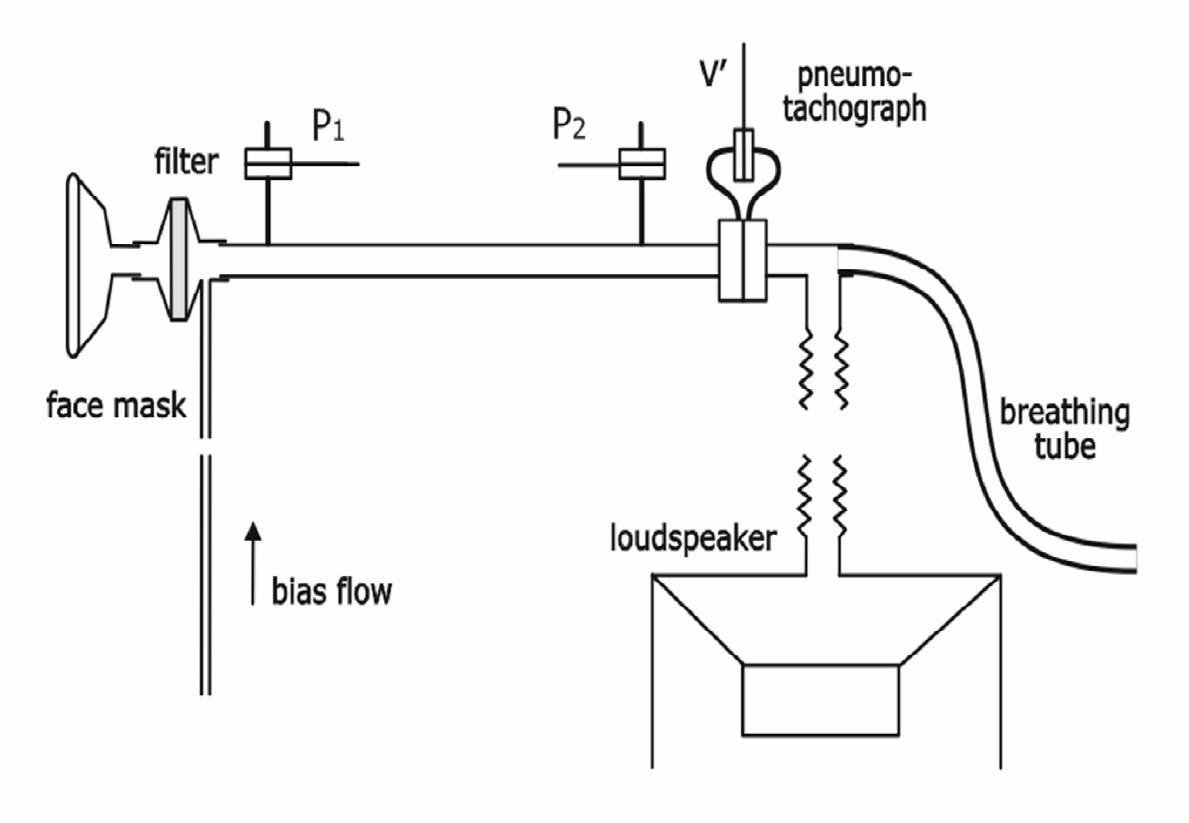

Figure 2. Schematic arrangement of the forced oscillatory impedance (Zrs) measurement. P_1, P_2: airway pressures; V': airflow

The subject was connected to the set-up via a silicone face mask (Figure 2.). The face mask was placed firmly over the newborn's mouth and nose to achieve a leak-free seal. P_1 and P_2 were measured with IC Sensors transducers (model 33NA002D, Miltipas, CA, USA). A screen pneumotachograph with another IC Sensors transducer was employed to record the spirogram. To enable spontaneous breathing of the subject, a wide-bore side-tube (with a high impedance for the high oscillatory frequencies and a low resistance against spontaneous breathing) was placed in parallel to the loudspeaker. A disposable bacterial filter was inserted between the face mask and the wave tube for hygienic purposes. In order to flush the dead space of the instrument, a bias flow of 2 l/min was maintained via the CO_2 sampling port of the filter.

Once the face mask had been positioned and the newborn had resumed the normal breathing pattern, 30-s oscillation intervals were recorded. The measurements were repeated, usually 6-to-10 times, until a steady state in the Zrs spectra was observed. The pressure (P_2) –

flow (V') loop and the spirogram were used for the detection of artefacts (leak around the mask, glottic closure, etc), and the affected recordings or parts thereof were discarded. The neonates often woke up during the measurements, which were resumed after soothing and mask repositioning. The average study time in a newborn was about 15 min.

Data analysis

Zrs was corrected for all instrumental impedances distal to the P_2 measurement point (filter, face mask, etc.). The spectra with the lowest reproducible Zrs values were selected for ensemble-averaging in each subject for each measurement day. The average Zrs data were fitted by a resistance (Rrs) - inertance (Irs) - elastance (Ers) model in the 12-to-32-Hz range (for average Rrs) and 8-to-32-Hz range (for Ers and Irs). From the latter parameters, the resonant frequency of the respiratory system (zero-crossing of Xrs, *f*res) was calculated as $f\text{res}=(1/2\pi)(E/I)^{1/2}$. The Zrs parameters obtained on the 3 subsequent days in the SVD and CS groups were analysed with 2-way repeated measures ANOVA.

4. RESULTS

4.1. Studies on macrosomic infants

A total of 5738 singleton births were included in the study from the 2-year period; 410 of the newborns were macrosomic, an incidence of 7.1%. The heaviest baby weighed 5500 g; he was born to a non-diabetic mother.

Among the mothers of the 410 macrosomic infants, 43 (10.5%) had diabetes: 9 (2.2%) were pre-gestational and 34 (8.3%) GDM. In the control group, 316 (6.6%) mothers had diabetes: 26 (0.5%) were pre-gestational and 290 (6.1%) GDM. The prevalence of maternal diabetes was significantly higher in the macrosomic group than in the control group (10.5% vs. 6.6%; $p<0.05$).

Table 1 summarizes the statistical data and analysis of the control and macrosomic groups.

The number of CS cases in the macrosomic group was 202 (49.3%), which was significantly more frequent ($p<0.001$) than in the control group: 1898 (39.9%). It was a very interesting finding that the male-female ratio among the macrosomic infants was 2.15 to 1, whereas in the control group it was 0.95 to 1. The difference was significant ($p<0.001$). As concerns the general condition of the macrosomic infants at birth, in 70 (17.0%) neonates the umbilical cord pH was <7.2, but most of them showed a quick recovery. Fortunately, only 4 (0.9%) of the 70 neonates had a 5-min Apgar score <7. NICU admission was needed for 21 (5.1%) patients, at either secondary or tertiary care; 21 (5.1%) had a respiratory disorder. Hypoglycaemia was found in 25 (6.1%) cases among the macrosomic infants, and 138 (2.9%) in the control group; the difference was significant ($p<0.001$). The incidence of polycythaemia did not differ significantly. As concerns the incidence of birth trauma, there was no significant difference in clavicle fracture or cephalhaematoma. There was a highly significant difference in the incidence of adrenal haemorrhage: 4 (0.98%) vs. 7 (0.15%); $p<0.001$. The only parameter which was significantly higher in the control group was the rate of hyperbilirubinaemia: 1446 (30.4%) vs. 76 (18.5%); ($p<0.001$). In both study groups, the perinatal mortality was zero.

The statistical comparison of congenital anomalies regarding their relation to the weight and diabetic history of the mother are detailed in Tables 2 A and B, without significant differences.

Statistical correlation analysis of the 4000-4499 g and ≥4500 g subgroups (Table 3) revealed significantly more cases in the higher weight group as regards an Apgar score <7 at 5 min, clavicle fracture, and NICU admission. In the case of polycythaemia, the correlation was very close to being significant.

The macrosomic neonates of diabetic mothers demonstrated a significantly higher incidence of hypoglycaemia, hyperbilirubinaemia and cardiomyopathy than did those of non-diabetic mothers (Table 4). The macrosomic infants of the non-diabetic mothers significantly more frequently exhibited a low umbilical cord blood pH (<7.2).

Table 1. Outcome measures of control group and macrosomic neonates

	Control	Macrosomic	p
Total	4757	410	
CS	1898 (39.9%)	202 (49.3%)	<0.001*
Males	2322 (48.8%)	280 (68.3%)	<0.001*
Umbilical cord pH <7.2	705 (14.8%)	70 (17.0%)	0.22
Apgar score <7 at 5 min	87 (1.8%)	4 (0.9%)	0.22
Congenital anomalies	185 (3.8%)	18 (4.3%)	0.68
Hypoglycaemia	138 (2.9%)	25 (6.1%)	<0.001*
Polycythaemia	161 (3.4%)	19 (4.6%)	0.19
Hyperbilirubinaemia	1446 (30.4%)	76 (18.5%)	<0.001*
Clavicle fracture	43 (0.9%)	7 (1.7%)	0.11
Cephalhaematoma	135 (2.8%)	15 (3.6%)	0.34
Adrenal haemorrhage	7 (0.15%)	4 (0.98%)	<0.001*
Respiratory disorder	305 (6.4%)	21 (5.1%)	0.26
NICU admission	210 (4.4%)	21 (5.1%)	0.58

Significance at $p<0.05$ is indicated by*.

Table 2A. Congenital malformations in the control and macrosomic groups

	Control n=4767	Macrosomic n=410	p
Congenital malformations	185 (3.9%)	18 (4.4%)	0.62

Table 2B. Congenital malformations of the macrosomic neonates of diabetic and non-diabetic mothers

	Diabetic n=43	Non-diabetic n=367	p
Congenital malformations	4 (9.3%)	14 (3.8%)	0.1

Table 3. Outcome measures of macrosomic subgroups

Outcome measures	BW		
	Group 1 4000-4499 g n=357	Group 2 ≥4500 g n=53	p
CS	170 (48%)	32 (60%)	0.08
Males	242 (68%)	38 (72%)	0.57
Umbilical cord pH < 7.2	60 (17%)	10 (19%)	0.71
Apgar score < 7 at 5 min	2 (0.6%)	2 (3.8%)	<0.03*
Congenital anomalies	14 (3.9%)	4 (7.5%)	0.23
Hypoglycaemia	20 (5.6%)	5 (9.4%)	0.28
Polycythaemia	14 (4.0%)	5 (9.4%)	0.07
Hyperbilirubinaemia	65 (18%)	11 (21%)	0.66
Clavicle fracture	3 (0.8%)	4 (7.5%)	<0.001*
Cephalhaematoma	12 (3.4%)	3 (5.7%)	0.41
Adrenal haemorrhage	3 (0.8%)	1 (1.9%)	0.47
Respiratory disorder	18 (5.0%)	3 (5.7%)	0.85
NICU admission	11 (3.1%)	10 (19%)	<0.001*
Mechanical ventilation	1 (0.3%)	1 (1.9%)	0.12
Cardiomyopathy	2 (0.6%)	1 (1.9%)	0.29
Neurological disorder	7 (2.0%)	2 (3.8%)	0.40

Significance at $p<0.05$ is indicated by *.

Table 4. Outcome measures of the macrosomic neonates of diabetic and non-diabetic mothers

	Diabetic n=43	Non-diabetic n=367	p
CS	23 (53%)	179 (49%)	0.56
Males	24 (56%)	256 (70%)	0.06
Umbilical cord pH < 7.2	2 (4.7%)	68 (19%)	0.02*
Apgar score < 7 at 5 min	0 (0%)	4 (1.1%)	0.49
Congenital anomalies	4 (9.3%)	14 (3.8%)	0.10
Hypoglycaemia	11 (26%)	14 (3.8%)	<0.001*
Polycythaemia	4 (9.3%)	15 (4.1%)	0.06
Hyperbilirubinaemia	13 (30%)	63 (17%)	0.04*
Clavicle fracture	0 (0%)	7 (1.9%)	0.36
Cephalhaematoma	3 (7%)	12 (3.3%)	0.22
Adrenal haemorrhage	1 (2.3%)	3 (0.8%)	0.34
Respiratory disorder	4 (9.3%)	17 (4.6%)	0.19
NICU admission	4 (9.3%)	17 (4.6%)	0.19
Mechanical ventilation	1 (2.3%)	1 (0.3%)	0.07
Cardiomyopathy	2 (4.7%)	1 (0.3%)	0.01*
Neurological disorder	1 (2.3%)	8 (2.2%)	0.96

Significance at $p<0.05$ is indicated by *

4.2. Comparison of oxidative stress markers in vaginal deliveries with or without epidural analgesia

Table 5 depicts the results of measurements relating to the oxidative stress and the activities of antioxidants. The oxidative stress represented by the level of LP was significantly lower in the EA group than in the control group (4.0 ± 1.5 vs. $6.5\pm1.8\times10^{-2}$ nmol/mg protein; $p<0.05$). As regards the antioxidants, the concentration of GSH (5.15 ± 0.48 vs. 7.75 ± 0.63 nmol/mg protein) was also significantly lower in the EA group ($p<0.05$). Of the antioxidant enzymes,

CAT exhibited a significantly lower activity (9.65±0.98 vs.14.08±1.2x10^{-4} BU/mg protein, $p<0.01$) in the EA group relative to the control group. The levels of SOD (2.68±0.36 vs. 3.2±0.38 U/mg protein) and GP (3.65±0.43 vs. 4.5±0.52x10^{-3} U/mg protein) were non-significantly lower in the EA group.

Clinical characteristics of the neonates in the two groups are presented in Table 6. The babies of mothers who received EA demonstrated a significantly lower arterial umbilical cord blood pH and a significantly lower BE. No cases with a 5-min Apgar score <7 were observed in either group.

Table 5. Levels of LP, GSH and activities of SOD, CAT and GP in the EA group relative to the control.

	Control n=50	EA n=36	p
LP	0.065±0.018 nmol/mg protein	0.04 ±0.015 nmol/mg protein	p<0.05*
GSH	7.75 ±0.63 nmol/mg protein	5.15 ±0.48 nmol/mg protein	p<0.05*
CAT	14.08±1.2×10^{-4} BU/mg protein	9.65±0.98×10^{-4} BU/mg protein	p<0.01*
SOD	3.2 ±0.38 U/mg protein	2.68 ±0.36 U/mg protein	p>0.05
GP	4.5±0.52×10^{-3} U/mg protein	3.65±0.43×10^{-3} U/mg protein	p>0.05

Significance at $p<0.05$ is indicated by *.

Table 6. Neonatal outcome measures for the control and the EA groups

	Control n=50	EA n=36	p
Umbilical cord blood pH<7.2	3 (6%)	13 (36%)	p<0.01*
Umbilical base excess <-12	10 (20%)	17 (47%)	p<0.01*
5-min Apgar score <7	0	0	

Significance at p<0.05 is indicated by *.

4.3. Neonatal lung function tests

Seven of 42 newborns were excluded from the study because of nasal congestion (n=3), face mask intolerance (n=3) or non-correctable leakage around the mask (n=1). No adverse events were noted during or following the measurements.

In the remaining 35 newborns, Rrs was characterized by a slight initial decrease with frequency, plateauing above 12-20 Hz, and an occasional rise above 32-36 Hz (Figures 3A and B). The mean value of *f*res was ~20 Hz, most likely reflecting the predominance of high-inertance nasal pathways.

The difference in Rrs between the SVD and CS neonates (mean±SD: 47.0±20.1 vs. 47.8±22.6 hPa.s/l) was not statistically significant (p=0.87). Likewise, there was no significant difference in Ers between SVD and CS (1617±730 vs. 1606±780 hPa/l; p=0.95).

Rrs and Ers exhibited large day-to-day fluctuations in ~40% of the newborns (Figures 4 and 5). In some of these subjects, very high values of Rrs and Ers were occasionally observed on one of the measurement days, whereas on other days their data were much lower and similar to those of the rest of the population. The 2-way repeated measures ANOVA did not reveal any systematic changes in the Zrs parameters during the 3 days. Interestingly, the pooled values of Ers and Rrs were highly correlated (r^2=0.742); this probably indicates unstable lung volumes, including very low ones where both Rrs and Ers are expected to increase. The pooled Irs and Rrs data also exhibited a close relationship (r^2=0.574), which

suggests that they are linked via the variable geometry of the large airways, and in particular that of the nasal pathways. Figures 6 and 7 illustrate the Ers vs. Rrs and the Irs vs Rrs relationships, respectively, with the regressions calculated separately for each measurement day.

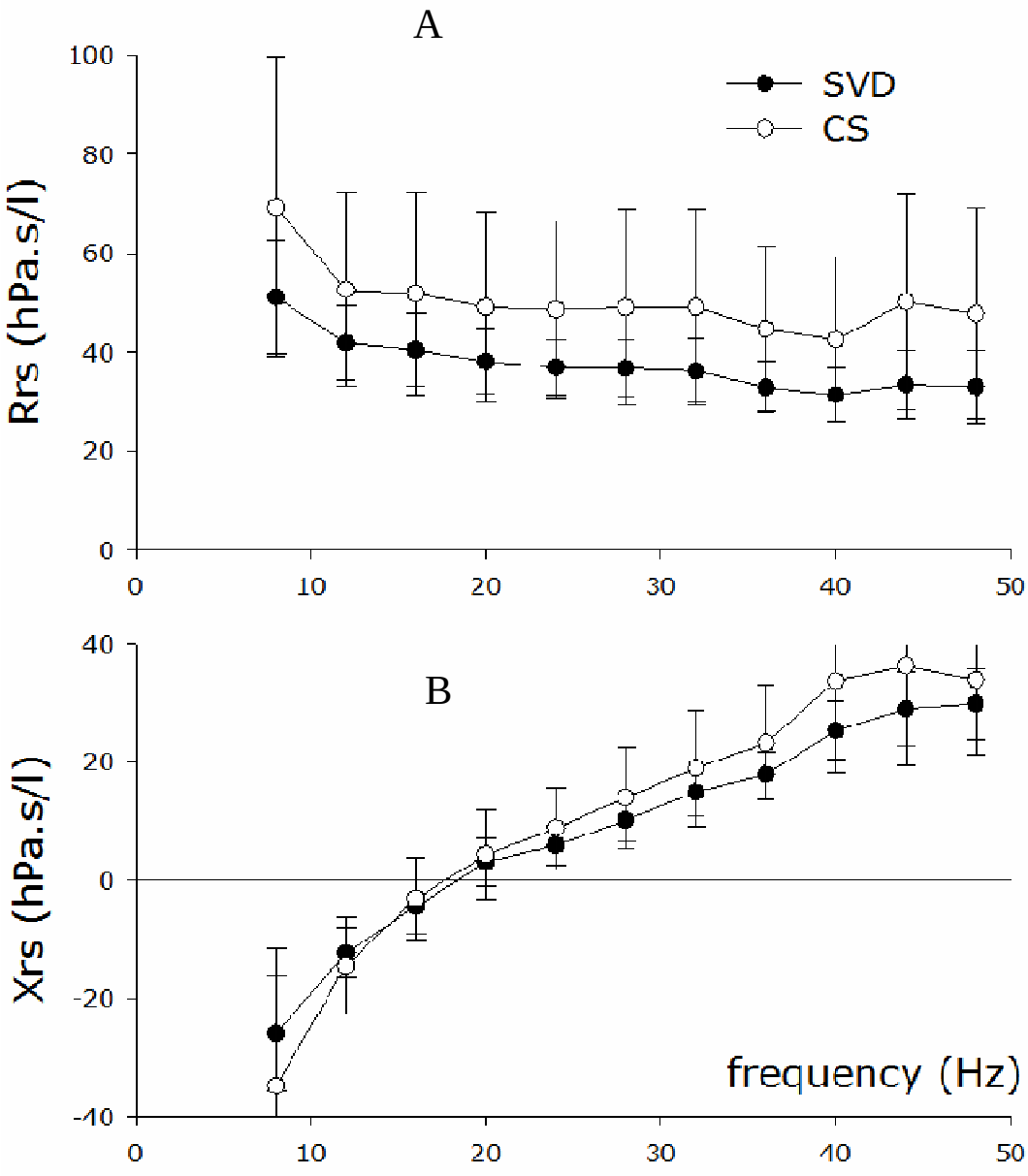

Figure 3. Frequency dependence of respiratory resistance (Rrs) (A) and reactance (Xrs) (B) in the medium-frequency range in newborns born by SVD or by CS.

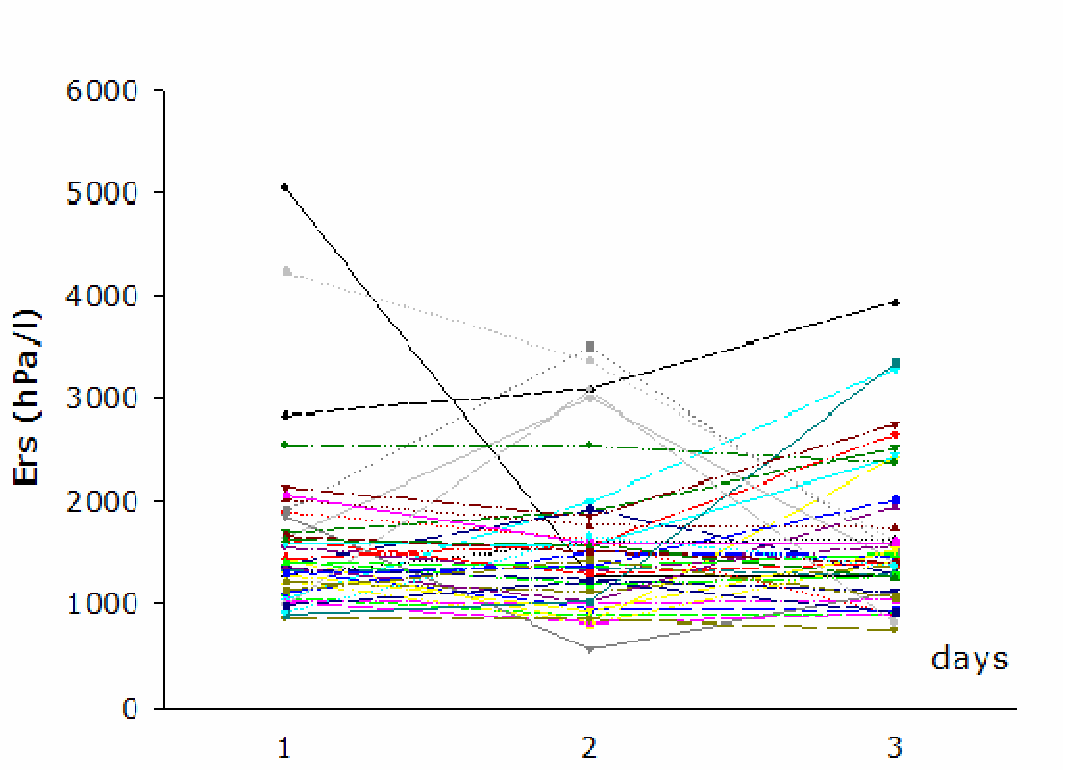

Figure 4. Changes in respiratory resistance (Rrs) in the 35 neonates in the postnatal 3 days.

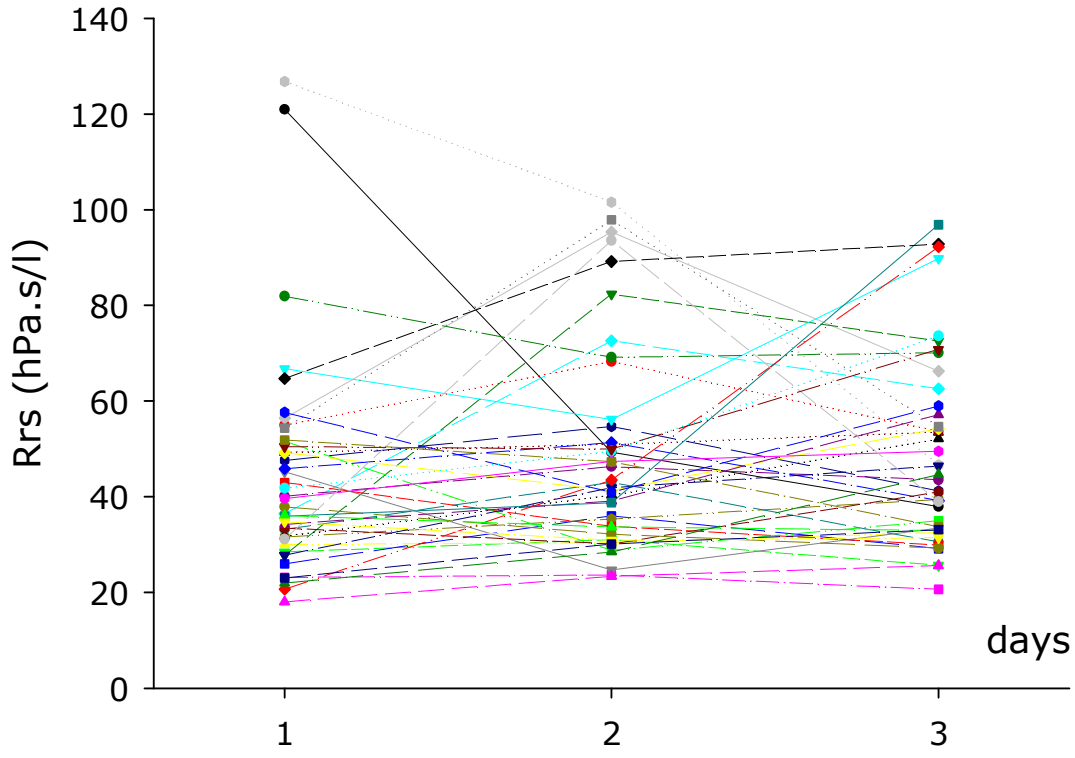

Figure 5. Changes in respiratory elastance (Ers) in the 35 neonates in the postnatal 3 days.

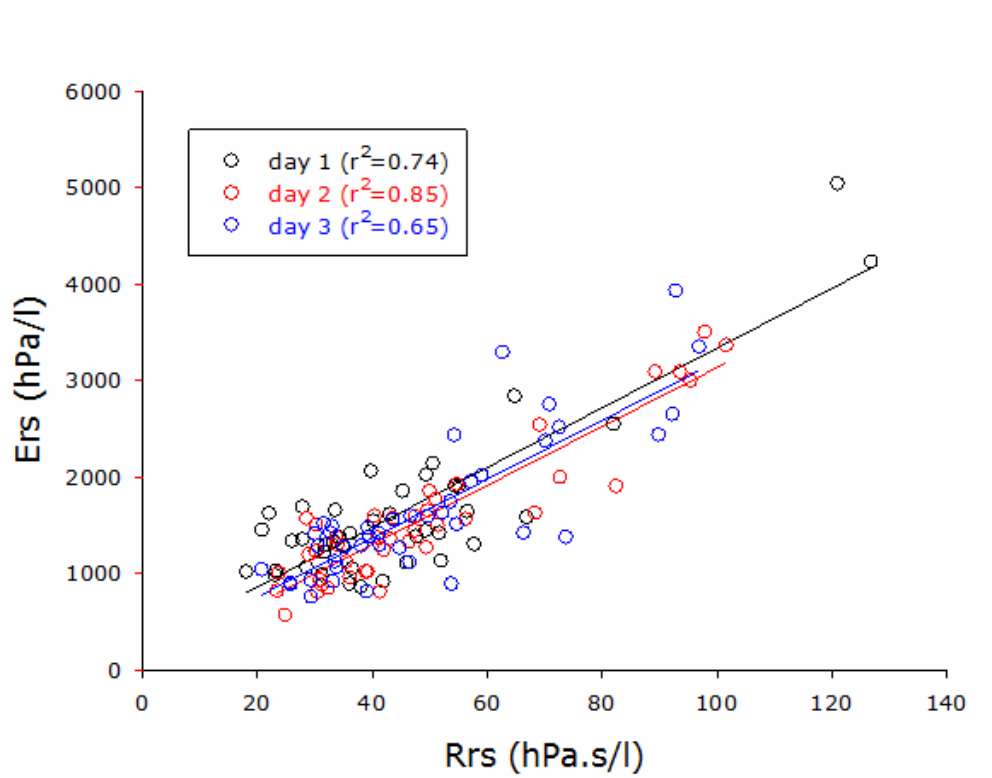

Figure 6. Relationships between elastance (Ers) and resistance (Rrs), with regressions and correlation coefficients (r^2) established for the 35 neonates on the individual measurement days.

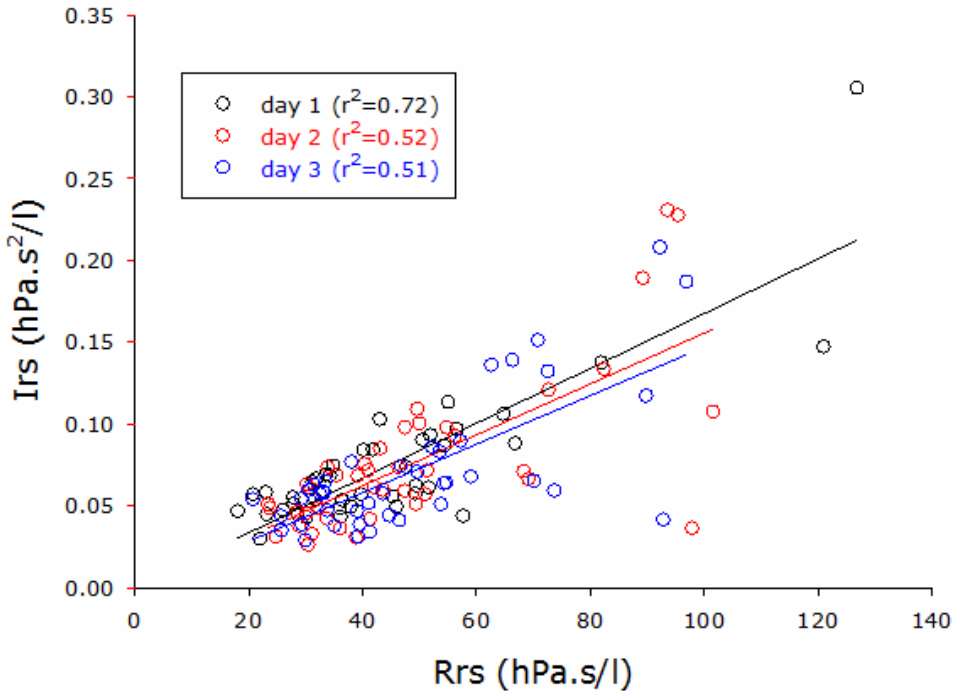

Figure 7. Relationships between inertance (Irs) and resistance (Rrs), with regressions and correlation coefficients (r^2) established for the 35 neonates on the individual measurement days.

5. DISCUSSION

5.1. Studies on macrosomic infants

Our findings regarding the neonatal outcome of macrosomic newborns, e.g. the higher incidence of CS, the male predominance and hypoglycaemia, were similar to those in previous reports; however, we found also that the prevalence of adrenal haemorrhage was significantly enhanced in the macrosomic group. All neonates with adrenal haemorrhage, even in the control group, were delivered by SVD. At our Department, each infant participates in an abdominal ultrasonographic screening programme, which helps provide reliable data on the occurrence of adrenal haemorrhage, even in those cases without symptoms. Adrenal haemorrhage, and especially the bilateral form, needs a further careful follow-up to prevent the later consequences. This finding highlights the importance of the abdominal ultrasonographic screening programme, especially for the macrosomic neonates born by SVD.

A significantly higher rate of hyperbilirubinaemia in the control group could be explained by the earlier deliveries (at a GA of 37 or 38 weeks) relative to the macrosomic group (40 and 41 weeks).

The macrosomic infants were born in good general condition, without serious birth trauma or brachial plexus paresis, but it should be borne in mind that the proportion of CS was significantly higher in the macrosomic group.

Furthermore, there were significantly more complications in the heavier macrosomic subgroup (≥4500 g) as concerns a more frequent low Apgar score at 5 min, clavicle fracture and NICU admission. This observation is consistent with the American experience of a sharp increase in adverse neonatal outcome above 4500 g [49].

Neonatal hypoglycaemia is a common problem in macrosomic infants; it is often associated with maternal diabetes. In our study, the incidence of hypoglycaemia was significantly higher in the macrosomic group and among the neonates of diabetic mothers. In this latter group, not only that of hypoglycaemia, but the incidence of hyperbilirubinaemia and cardiomyopathy were also increased.

Glycaemic control of the diabetic pregnant is important, as any abnormal elevation of HbA1C increases the risk of teratogenesis [50]. In our macrosomic group, the incidence of

congenital anomalies was 4.4%, in comparison with 3.9% in the control group, without a significant difference, showing that these mothers presumably had undergone appropriate diabetic control. The comparison of the incidence of congenital anomalies between the macrosomic infants of diabetic (9.3%) and non-diabetic mothers (3.8%) resulted in a very close to significant relation (p=0.1).

The male to female ratio was significantly higher in the macrosomic group. The consistency of this observation across different populations is striking. Various hypotheses have been put forward to explain the cause of this phenomenon and it is very likely that there is a gender-specific gene that affects insulin sensitivity [51]. The more insulin-resistant female fetus is less responsive to the trophic effect of insulin and more susceptible to type 2 diabetes mellitus. This increase could also be due to the action of testicular hormones.

The limitation of our study is its retrospective nature; this is why the data relating to the exact indications of CS were not recorded. It is also important to note that the maternal choice was not taken into account in the decision for CS in our Department. Moreover, a detailed medical follow-up of the sick neonates was not feasible as they were transferred to another department.

Several previous studies have already revealed the most frequent neonatal complications, such as shoulder dystocia, brachial nerve palsy, clavicle facture and birth asphyxia [52, 53], but the increased incidence of adrenal haemorrhage among macrosomic newborns born by SVD has not been investigated earlier, to our knowledge.

Modern obstetric and neonatal care has substantially reduced many of the problems previously seen in these infants, but macrosomia continues to deserve attention because of the associated risks of morbidity. For a further reduction of the problems, a better understanding of the root cause of macrosomia is needed. Each woman, whose fetus is diagnosed as weighing more than 4500 g, even if the prediction of macrosomia is inaccurate [54], should be fully informed of the risks related to macrosomia for herself and the baby. Moreover, these macrosomic infants should always participate in a very careful medical follow-up for the timely recognition of possible problems.

5.2. Comparison of oxidative stress markers in vaginal deliveries with or without epidural analgesia

RBCs from neonates born by SVD with the use of EA were found to display significantly less oxidative stress, but they also had significantly lower levels of antioxidant parameters relative to the neonates who underwent SVD without maternal pain relief. On the other hand, these neonates also exhibited a lower cord blood umbilical pH and a lower BE. EA seemed to reduce the level of oxidative stress; however, these neonates more frequently exhibited acidosis with a quick recovery, without consequences in the later neonatal period.

Several previous studies have reported that the provision of systemic pain relief with meperidine was associated with more pronounced acidosis as compared with EA [55], but the available data regarding the impact of the delivery mode on the level of oxidative stress in the fetal circulation are inconsistent [56, 57].

We presume that elevations in stress and antioxidant parameters are normal physiological responses to the process of birth. This stress could therefore be necessary in the natural process of uncomplicated pregnancies for both the fetus and the mother. In the following, we briefly summarize the most important aspects of this issue. First of all, it has been concluded in several articles that there is a significant relationship between pain and oxidative stress both in animal models and even in preterm infants [58-60]. Accordingly, pain enhances the level of oxidative stress during delivery in both mother and fetus. This increased level of oxidative stress during delivery naturally induces the antioxidative defence mechanism.

As regards the fetus, there is another interesting maturation phenomenon which must be mentioned here. If labour occurs at term rather than earlier, it triggers a compensatory up-regulation of the non-enzymatic antioxidant reserve. This up-regulation could be a benefit of term labour that protects the newborn from the relative hyperoxia at delivery.

Numerous articles have investigated the effects of different forms of anaesthesia on the oxidative balance, and the literature seems to agree on the fact that local anaesthetics have a potential antioxidant effect [61]. In considering these data, it should be underlined that these agents could have attenuated the oxidative stress and enhanced the levels of antioxidants in the EA group; therefore, they could have influenced the differences between our two groups. Unfortunately, as both the mechanism of action of painkiller drugs and the process of pain

relief result in antioxidative effects, one cannot separate the underlying causes; only their combined effects are measurable.

Nevertheless, interestingly enough, the moderation of stress-induced damage through the administration of EA could also be beneficial. Preterm or IUGR infants are especially susceptible to ROS-induced damage, since the state of their antioxidant defence is premature, and their ability to increase the synthesis of antioxidants in response to hyperoxia or other oxidant challenges is inadequate [62].

Our results suggest that EA plays a dual role as concerns oxidative stress, tending to attenuate oxidative stress, but also decreasing the level of antioxidants. However, the neonates born to mothers who had received EA manifested acidosis more frequently in the first few minutes of their extrauterine life. Further investigations are definitely needed to evaluate the possible association between the attenuation of oxidative stress and the acid-base balance and on the impact of the modulation of oxidative stress during birth.

5.3. Neonatal lung function tests

We present the first study on airway and tissue mechanics achieved by using the FOT in a group of unsedated newborn term infants during quiet sleep. Neither the difference in Rrs nor in Ers between the SVD and CS neonates were statistically significant, however, we concluded that a high success rate could be achieved in the measurement of Zrs in healthy newborns; the Zrs data obtained with this technique are physiologically meaningful and of potential importance in monitoring the lung function in the first few days of life.

Pulmonary function tests play a major role in paediatric clinical practice and are of prime importance for diagnosis, monitoring disease progression, and assessing the effectiveness of therapies. Albeit spirometry remains the principal means by which the lung function is assessed in most clinical settings, interest in the use of other, more specific techniques is also growing rapidly.

Associations between various FOT parameters and chronic lung disease have already been published in the literature [63], but we are unaware of any study on healthy term newborns.

The FOT is a technique of promise as it has reached a high level of sophistication. Spirometry involves the subject making forced expiratory manoeuvres following deep inspiration, while the air flow at the mouth is measured. The significant shortcoming of this technique is the vigorous manoeuvre required from the patient, which excludes its application in children under the age of 4 years, or in patients with a neuromuscular or cognitive deficit. The raised volume rapid thoracic compression technique [64] is capable of simulating the forced expiratory manoeuvre and it has also been employed in infants; however, it cannot be accomplished without sedation. Moreover, while it may be sensitive to the presence of lung disease, it lacks specificity and is difficult to link to structure. Mechanical impedance as provided by the FOT, on the other hand, has potential advantages in this regard, for it contains a great deal of information about the link between lung structure and function [65].

Zrs has mostly been measured in humans over the intermediate frequency range from 4-6 Hz to 20-30 Hz [66], where the forced oscillatory recordings are not corrupted by harmonics from spontaneous breathing as they are at lower frequencies. Impedance measurements over this frequency range provide estimates of parameters such as resistance, elastance (compliance), and resonant frequency, all of which are potentially discriminatory in disease. In healthy adult subjects, Rrs is virtually independent of frequency, while Xrs is initially negative, but increases rapidly until it crosses the frequency axis at the resonant frequency (at or above 10 Hz), after which it increases almost linearly with frequency [67]. In the current study, the frequency range was selected between 8 and 48 Hz; in this frequency interval, Rrs was characterized by a slight initial decrease with frequency and plateauing above 20 Hz, where the resonance in Xrs was also observed. Overall, this frequency range is roughly one octave above the range usually covered in Zrs measurements in adults, and it reveals similar features of Zrs. Specifically, the initial fall in Rrs with frequency can be attributed to the decreasing contribution of the tissue resistance, whereas the occasional higher-frequency rise in Rrs reflects the involvement of an airway rheology component unrelated to the regime of spontaneous breathing (these are the reasons why the mean Rrs was calculated between 12 and 32 Hz in the present study). The frequency range for the estimation of Ers and Irs was also terminated at 32 Hz, in order to have balanced contributions of the elastic and inertial properties to Xrs.

Since studies on respiratory mechanics in healthy newborns are very scanty, and those obtained with the FOT are apparently unavailable, the Zrs parameters established in the

current investigation are difficult to interpret in the context of paediatric respiratory mechanical data.

The reproducibility of Zrs in healthy humans has previously been shown to be similar to that observed in other parameters of respiratory mechanics such as those provided by body plethysmography or the flow interrupter technique. According to the literature, both the short-term and the day-to-day variabilities in Rrs measured by the FOT in healthy subjects ranged from 5% to 30%, depending on the technique used and the population studied [68]. Klug and Bisgaard [69] reported a within-test variation of Xrs between 16% and 17%. Few studies have assessed the between-test reproducibility in young children, with one report of a similar within- and between-test repeatability of approximately 6% [70]. The day-to-day and weekly reproducibility in older children appear to be similar, with values of approximately 16–17% [71,72]. Lødrup Carlsen et al. [73] studied awake infants at an average age of 2.9 days with the single-breath occlusion technique, and observed within-subject variabilities of 17.8 and 23.1%, respectively, for Ers and Rrs. We are unaware of any other previous report on the changes in respiratory mechanics in the first few days of life. In our measurements, made on consecutive days, the within-subject variability was 22.9±15.8% for Rrs and 25.4±21.1% for Ers. However, both Rrs and Ers exhibited large day-to-day changes in ~40% of the newborns, most probably because of the inborn variability of the end-expiratory lung volume. Additionally, the ~15 min average study time may not have been long enough for the minimum Zrs to be observed in these subjects.

Rrs in children has been reported to have a sensitivity of 69% and a specificity of 78% [74]. Several studies have provided reference values for Rrs and Xrs in healthy subjects [75]. These data are generally consistent, although some differences exist because of varying population characteristics and differences in methodological details (the characteristics of the measuring device, the type of forced oscillation signal used, and differences in data processing procedures). In adults, Zrs is a function mainly of gender, weight, height and age [76]. Standardization of the measurement conditions for lung function testing is a crucial issue for the infant`s safety and the accuracy of the test. Recommendations have been developed by the American Thoracic Society/European Respiratory Society Working Party [66] and the specific preparation measures for the FOT and details of the methodology have been described [77, 78].

The FOT is currently gaining acceptance in the assessment of paediatric patients, in part because it requires little to no cooperation, which has led to its extensive use in infants and young children [79]. Zrs has been reported to have useful diagnostic possibilities in a wide variety of paediatric diseases, including asthma, cystic fibrosis, bronchopulmonary dysplasia and neonatal lung diseases. The FOT is most often used in an out-patient setting for routine diagnosis and monitoring, but it has been shown to have potential for helping in the management of acute attacks of asthma; it correlates with spirometry [80]. A number of studies have reported forced oscillatory parameters from healthy children in the 2- to 5-year age group. The majority of these have reported Rrs alone, with little information on the behaviour of Xrs with growth and development. There is some variability in the reported Rrs values and differences in equipment and methodology, and lack of standardization to this point may have contributed to some of this spread. The majority of studies have described an inverse relationship between Rrs and height, with no significant differences between genders.

More recently, attempts have been made to measure impedance at lower frequencies. This allows for the discrimination between the overall resistance of the conducting airways and the dissipative properties of the lung periphery. Use of this frequency range, however, also requires a greater degree of patient cooperation, such as a voluntary breath hold, and its usefulness as a routine clinical test is therefore still somewhat open to debate. Nevertheless, measures of parenchymal mechanics derived from low-frequency impedance have been found to correlate with inflammation in cystic fibrosis and to be altered following a methacholine challenge in infants [81]. Novel applications of forced oscillation technique in the clinical setting among adults include the monitoring of respiratory mechanics during mechanical ventilation and sleep [82].

The FOT is particularly promising for use in infants, for whom few alternatives exist for measuring lung function. Here, however, getting the imposed oscillations in flow past the upper airways poses a particular challenge in terms of instrumentation. In our study, a face mask was used to connect the infant to the set-up. The use of a mask gives rise to potentially significant shunt impedances; Zrs measurements include the rather high nasal resistance and are subject to artifacts from mask leak. Nevertheless, these practical challenges have not prevented the FOT from providing valuable physiological information about the newborns' lungs.

One of the great advantages of the FOT for assessing the respiratory mechanical function is that it is completely non-invasive. The primary aim of any lung function test is to provide information allowing the accurate separation of healthy subjects and those individuals with underlying airway pathology. Measurements of lung function are feasible in unsedated newborns, the FOT being used to gain important knowledge about respiratory mechanics in the developing lung.

6. CONCLUSIONS

CS is an effective intervention to reduce maternal and neonatal mortality relative to SVD, when it is medically justified. Newborn and maternal mortality are closely linked, and therefore the risks can be mitigated with quality care during pregnancy, safe delivery by a skilled attendant, and immediate postnatal care, including resuscitation, extra care of low birth weight babies, attention to baby warmth, treatment of neonatal sepsis and early initiation of breastfeeding.

Our research, firstly focusing on macrosomic neonates, revealed an expected higher incidence of CS; these macrosomic infants were born in good general condition without serious adverse outcomes. Moreover, we highlighted the increased incidence of adrenal haemorrhage among the macrosomic neonates born by SVD.

Secondly, we compared the levels of oxidative stress in SVD with and without maternal EA, in spite of the fact that the amount of stress which is useful in the process of birth is still unknown.

The third part of our work was to evaluate the lung function in the first few days of life. We presented the first study in Hungary of successful measurements of airway and tissue mechanics in healthy newborns during quiet sleep, which could be helpful in future in the earlier detection of pulmonary abnormalities, but further studies are definitely needed.

7. ACKNOWLEDGEMENTS

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9. ÖSSZEFOGLALÁS

Bevezetés

A császármetszés (CS) klinikai gyakorlatba való bevezetése a kezdeti időkben elsősorban az anyai és a magzati élet megmentésére szolgált. Míg az 1930-as években a CS aránya Magyarországon 0,5% alatt volt az összes szülések számát tekintve, ez az arány az 1970-es évek elejétől kezdve megdöbbentő emelkedést mutat, 2009-re már meghaladta a 30%-ot. Hasonló tendencia figyelhető meg az Amerikai Egyesült Államokban. Ezzel együtt, a CS anyai és újszülöttet érintő kockázatairól számos szakirodalmi közlés látott napvilágot, kiemelve a különböző rizikócsoportokat, köztük a macrosom újszülötteket. Az összehasonlítás nehézsége abból adódik, hogy a macrosomia definíciója nem egységes, egyrészt a gesztációs időre, nemre, rasszra vonatkoztatott 90 ill. 97 percentilis vagy a 2SD feletti - másrészt a terhességi kortól függetlenül a 4000, 4500 vagy 5000 g feletti születési súly esetén beszélhetünk macrosomiáról. A kérdés azért is aktuális, mert a macrosomia előfordulása növekvő tendenciát mutat az utóbbi évtizedekben, 5-20% incidenciával, földrajzi területenként eltérően.

A gyakoribb CS mellett a per vias naturales (PVN) szüléseknél is ma már jogos elvárás a fájdalomcsillapítás valamilyen formája. Az anyára és az újszülöttre biztonságos epidurális érzéstelenítés (EA) élettani és farmakológiai hatásainak tisztázása az eljárás még szélesebb körű alkalmazása szempontjából kívánatos. Nem elhanyagolható kérdésként merül fel, hogy miként befolyásolja a fájdalomcsillapítás ezen módja a születés során elkerülhetetlen oxidatív stressz folyamatát. A magzat megszületését követően egy számára relatív hyperoxiás környezetbe kerül, s az oxidatív stressz során képződő reaktív oxigén intermedierek megbontják a sejtek pro- és antioxidáns egyensúlyát, ezzel segíthetik is az extrauterin adaptációt, de veszélyt is jelenthetnek.

A neonatológiában kitüntetett szerepe van a légzésélettani és patológiai folyamatok nyomonkövetésének. A szakirodalomban meglepően kevés adatot találunk egészséges érett újszülöttek légzésfunkciós adatairól, egységes normálértékekről nincs ismeretünk. Az azonban ismert, hogy a születéskori tüdőfunkció befolyásolhatja a későbbi légzőrendszeri betegségek kialakulását vagy akár annak súlyosságát. Bár jelentős kutatások folynak az újszülött- és csecsemőkori légzésmechanika terén, e vizsgálatok legtöbbször patológiás esetekben, pl. gépi lélegeztetés során történnek, vagy szedációt igényelnek. Az 1956-ban

DuBois által először leírt kényszerített oszcillációs technika (Forced Oscillation Technique : FOT) segítségével kis amplitúdójú gerjesztőjel alkalmazásával vizsgálható a légzőrendszeri mechanikai impedancia (Zrs). E módszer továbbfejlesztett változata kínált lehetőséget először egészséges újszülöttek vizsgálatára.

Célkitűzés

- Macrosom újszülöttek születési módjának, neonatológiai adatainak és korai szövődményeinek vizsgálata összehasonlítva normál születési súlyú újszülöttekkel.
- Oxidatív stressz paraméterek és sav-bázis értékek elemzése artériás köldökzsinórvér mintákból PVN szülések esetén, összehasonlítva az epidurális érzéstelenítésben részesült és a fájdalomcsillapításban nem részesült egészséges anyák újszülöttjeinek két csoportját.
- Terminusban született, egészséges, 1-3 életnapos újszülöttek légzésmechanikájának FOT-tal történő mérése szedáció alkalmazása nélkül, Zrs meghatározása PVN és CS útján született újszülöttekben.

Anyag és módszer

Macrosom újszülöttek vizsgálata

Retrospektíve a 2008. jan. 1. és 2009. dec. 31. között egyes terhességből a 37. és 41. hét között a klinikánkon született, >2500 g születési súlyú újszülöttek adatait elemeztük. A 2500-3999 g közöttieket tekintettük kontrollnak, míg a 4000 g és felettiek képezték a macrosom újszülöttek csoportját. Ez utóbbin belül külön vizsgáltuk a 4000-4499 g közötti- és a 4500 g felettiek adatait. Az újszülött állapotára vonatkozó paraméterek közül a köldökzsinór pH-t és az 5 perces Apgar-értékeket, valamint a gyakoribb neonatológiai adatokat elemeztük. A statisztikai analízis a χ^2 próba alkalmazásával történt, szignifikáns összefüggésnek a $p<0,05$ értékű eredményt tekintettük.

Oxidatív stressz paraméterek összehasonlítása

Ebben a prospektív vizsgálatban panaszmentes, egyes terhességből, terminusban született 86 egészséges újszülött és ezek édesanyja szerepelt: az EA csoportban 36, a kontrollban 50. Kizáró tényező volt az anya vagy a magzat bármilyen gyógyszeres kezelése, betegsége, hüvelyi szülésbefejező műtét vagy császármetszés. Közvetlenül születés után a köldökzsinór artériás vérből meghatároztuk annak pH és basis excess (BE) értékét, majd az

antioxidáns glutation (GSH), szuperoxid-dizmutáz (SOD), kataláz (CAT), glutation-peroxidáz (GP) szinteket, valamint az oxidatív stressz mértékét jelző lipid peroxidácót (LP). A statisztikai analízis Student féle t-próbával történt.

Újszülöttkori légzésfunkció mérése

Prospektív vizsgálat során klinikánkon 42 egyes terhességből, terminusban született (PVN=19, SC=23) egészséges, tünetmentes újszülött légzőrendszeri Zrs meghatározása történt FOT-tal természetes alvás alatt, etetést követően, az első 3 életnapon. A vizsgálat alatt a vitális paramétereket és az O_2 szaturációt monitorizáltuk. Alacsony amplitúdójú (<2 hPa) álvéletlen kényszerített oszcillációt a 8-48-Hz frekvenciatartományban számítógépvezérelt hangszóróval generáltunk, és ezt szuperponáltuk a spontán légzésre. A Zrs mérését az ún. hullámcső-technikával, a spirogram felvételét pedig pneumotachográfiával végeztük. Az átlagos vizsgálati idő újszülöttenként 15 perc volt, melyben 5 - 7, egyenként 30 s hosszú felvételt, s ezekből spirogramot is készítettünk. A Zrs frekvenciafüggését több légzési ciklus átlagértékeként mértük, és a Zrs spektrumokból modellillesztéssel határoztuk meg a légzőrendszer rezisztív (Rrs), elasztikus (Ers) és inertív (Irs) paramétereit. A Zrs értékek oszcillációs frekvenciától való függését a PVN és SC útján született újszülöttekben, valamint a Zrs paraméterek intraindividuális, az első 3 életnap során bekövetkező változásait a kétutas ismételt méréses ANOVA módszerrel értékeltük ki.

Eredmények

Macrosom újszülöttek vizsgálata

A vizsgált két év alatt 5738 újszülött felelt meg a beválogatási kritériumoknak, ebből 410 (7,1%) volt macrosom. Az anyai cukorbetegség prevalenciája szignifikánsan magasabb volt a macrosom csoportban a kontrollhoz képest (10,5% vs. 6,6%). A császármetszések száma a macrosom csoportban 202 (49,3%), ami szignifikánsan gyakoribb a kontroll csoporthoz képest (1898; 39,9%). A fiú-leány arány a macrosom csoportban 2,15:1,0; ezzel szemben a kontroll csoportban gyakorlatilag megegyező volt (0,95 : 1,0), ami szintén szignifikáns különbség. A macrosom újszülöttek közül 70-nek (17,0%) volt a köldökzsinór vér pH-ja 7,2 alatti, de csak 4-nek (0,9%) volt 7 alatt az 5 perces Apgar-értéke. II. vagy III. szintű intenzív újszülött osztályos (NIC) felvételre 21 (5,1%) esetben került sor, s szintén 21 (5,1%) újszülött igényelt légzéstámogatást. Hypoglycaemia 25 esetben (6,1%) fordult elő a macrosom újszülöttek között, míg a kontroll csoportban ez szignifikánsan kevesebbszer (138;

2,9%). A szülési sérülések közül nem volt számottevő különbség a kulcscsonttörés és a cephalhaematoma gyakoriságában, a mellékvesevérzés viszont szignifikánsan magasabb arányban fordult elő a macrosom újszülöttek között (4; 0,98% vs. 7; 0,15%). A macrosom csoporton belüli alcsoportokat összehasonlítva a 4500 g felettiekben szignifikánsan gyakoribb volt a kulcscsonttörés, a 7-nél alacsonyabb 5 perces Apgar-érték és az újszülött intenzív osztályos felvétel előfordulása. A diabéteszes és nem-diabéteszes anyák macrosom újszülöttjeit összehasonlítva statisztikailag szignifikánsan több volt a hypoglycaemia, hyperbilirubinaemia és cardiomyopathia a diabéteszes csoportban.

Oxidatív stressz paraméterek összehasonlítása

Az oxidatív stressz mértékét mutató LP szignifikánsan alcsonyabb volt az EA csoportban a kontrollhoz képest (4,0±1,5 vs. 6,5±1,8x10^{-2} nmol/mg protein). Az antioxidánsok közül a GSH (5,15±0,48 vs. 7,75±0,63 nmol/mg protein) és a CAT (9,65±0,98 vs. 14,08±1,2x10^{-4} BU/mg protein,) enzimaktivitás értéke szignifikánsan alacsonyabb volt az EA csoportban a kontrollhoz képest. A SOD (2,68±0,36 vs. 3,2±0,38 U/mg protein) és a GP (3,65±0,43 vs. 4,5±0,52x10^{-3} U/mg protein) szintje is alacsonyabb volt az EA csoportban, de ez a szignifikancia határát nem érte el. Az EA csoportba tartozó újszülöttekben az artériás köldökzsinórvér pH és BE értéke szignifikánsan alacsonyabb volt, mint a kontrollokban.

Újszülöttkori légzésfunkció mérése

42 közül 7 újszülöttet zártunk ki a vizsgálatból, nehezített orrlégzés (3 eset), arcmaszk intolerancia (3 eset), vagy arcmaszk melletti levegőszökés (1 eset) miatt. A vizsgálat alatt vagy azt követően nemkívánt reakciót nem észleltünk. A Zrs frekvenciafüggése az egészséges felnőttekéhez hasonló lefutású volt egy oktávval magasabb transzpozícióval, a kezdeti csökkenést 12-20 Hz körüli plató követte, a PVN és a CS csoportok között a frekvenciafüggésben nem volt különbség. A PVN és CS-val született újszülöttek között nem volt szignifikáns eltérés az Rrs (47,0±20,1 vs. 47,8±22,6 hPa.s/l) és az Ers (1617±730 vs. 1606±780 hPa/l) tekintetében sem. Az 1., 2. és 3. életnapon ismételt mérések során az Rrs és Ers paraméterek az újszülöttek ~40 %-ában jelentős, napról-napra történő ingadozását tapasztaltuk.

Megbeszélés

Macrosom újszülöttek vizsgálata

A macrosom újszülöttek, kevés kivételtől eltekintve, jó általános állapotban születtek, súlyos szülési sérülés nem fordult elő, aminek hátterében a fokozott odafigyelés ill. a CS szignifikánsan magasabb aránya állhat. Ennek ellenére rá kell irányítani a figyelmet az általunk észlelt mellékvesevérzés gyakoribb előfordulására a PVN született macrosom újszülöttek között. Egyértelmű eredményként könyvelhetjük el, hogy a modern szülészeti és gyermekgyógyászati klinikai gyakorlat a macrosom újszülöttek korábban észlelt súlyosabb szövődményeinek előfordulását jelentősen csökkentette. Mindemellett továbbra is kiemelt figyelmet igényel elsősorban a 4500 g-ot is meghaladó testtömegű újszülöttek világrahozatala és közvetlen neonatológiai ellátása, melyben a szakmai protokollok betartása mellett individuális helyzetfelismerésre és összehangolt, multidiszciplináris teammunkára van szükség.

Oxidatív stressz paraméterek összehasonlítása

Az epidurális érzéstelenítésben részesült anyák újszülöttjei az oxidatív stressz enyhébb fokát mutatták, mint a fájdalomcsillapításban nem részesülteké, ugyanakkor, az antioxidáns szintjük a vizsgált paraméterek alapján alacsonyabb volt, s szignifikánsan gyakoribbnak mutatkozott az acidózis előfordulása - klinikai szövődmények nélkül – ebben a csoportban. A csökkent lipidperoxidáció ugyan kedvezőnek tűnik, mégsem szabad megfeledkezni a mérsékeltebb antioxidáns kapacitásról, ami – többek között - a hypoxiás állapotokat követő reperfúziós oxidatív stressz elhárításában jelentőséggel bírhat. Mérési eredményeink továbbra is rámutatnak, hogy keresni kell az optimális arányt a szükséges oxidatív stressz és annak kompenzálási mechanizmusai között.

Újszülöttkori légzésfunkció mérése

Születést követő első napokban történő légzésfunkciós vizsgálatokat elsőként alkalmazva újabb ismereteket nyertünk egészséges újszülöttek légzőrendszeri állapotáról. Összehasonlítottuk a PVN ill. CS útján világrajött újszülöttek légzésmechanikai adatait, elsősorban az irodalomban ismert CS-t követő légzészavarok gyakoribb incidenciájának saját módszerünkkel történő ellenőrzése céljából. Jelen vizsgálatban nem találtunk e két csoport légzőrendszeri paraméterei között szignifikáns különbséget. Új légzésfunkciós normál értékek meghatározása elengedhetetlen a patológiás állapotokkal való összehasonlításhoz. Mérési eredményeink ezenfelül a neminvazív vizsgálatok iránti növekvő igény miatt is előremutatóak, a módszer klinikai értékének felbecsüléséhez további vizsgálatok szükségesek.