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Efficient, Simple and Inexpensive Program for Prevention of Very Early Prematurity

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Infants who are born prematurely (< 37+0 gw) and/or have a low birthweight (< 2500g) suffer a higher risk of mortality and morbidity. Particularly those infants are at considerable risk, who are born very prematurely with less than 32+0 gw and those whose birthweight is very low, less than 1500g. Although in industrial countries neonatologists have achieved enormous success in keeping extremely premature infants alive, mortality increases rapidly with decreasing birthweight. The immediate and longterm sequelae of prematurity are also alarming (1, 2, 8-10) - something which is sometimes neglected when just measuring the "successes" of modern intensive care by mortality rates.

Also the general financial expense is enormous. Lewit and cow. (6) estimated that in 1988 in the USA each year the costs of medical care, child care and education for the 3.5 - 4 million children aged up to15 years, who had been born with low birthweight, were between 5.5 and 6 billion (US)-Dollars more than they would have been if those chil-dren had been born with normal birthweight.

Causes of late abortion and prematurity

A large number of reasons are known to cause late abortions and prematurity. Lockwood and Kuczynski (7) divided most of the known causes of prematurity into four pathogenetic processes:

- activation of the maternal or fetal hypothalamic-pituitary-adrenal (HPA) axis
- decidual-chorioamniotic or systemic inflammation
- decidual hemorrhage
- pathological distension of the uterus.

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Infection is the main cause of preventable prematurity

As far as the avoidable causes are concerned, infections play the main role: ascending genital infection is known to be the main source - particularly of premature births below 32+0 gw. Back in 1991 (11, 12) we were able to find concrete signs of an infection in about three quarters of the infants with a birthweight of less than 2000g. The amount of cases with premature rupture of membranes, was correspondingly high, namely 55%. The association between bacterial vaginosis and prematurity is particularly remarkable. Maternal urinary tract infections or systemic infections can however, also lead to premature birth.

Prematurity is increasingly preventable

There is a common saying: "prevention is better than cure". Therefore,

- the best is screening for causes that may lead to prematurity and to treat them as early as possible, rather than
- looking for and treating symptoms that indicate the threat of prematurity, which are already present;
- the poorest solution is the treatment of extremely premature infants with modern intensive care.

Our prematurity-prevention-program

After having been engaged in this field for 30 years, in 1989 we developed a new prematurity-prevention-program. The original part with its 4 stages is intended for physicians. Considering the allotted space for this contribution, it is not possible to go into the details, but this whole concept has been published repeatedly (11, 12, 15). Detailed information about the program is also on our website (s. authors' address) The main emphasis of our program lays in screening each pregnant woman

for pre-infection signs - or if this has been started too late, for infection signs - because disturbances of the vaginal milieu and infections can be treated more successfully if they are diagnosed at a very early stage. In cases of other prematurity causes, the possibility of intervention and successful therapy is clearly not so good.

The measurement of the vaginal pH-value is particularly important. An increase in the pH-value can refer to

- a disturbance in the vaginal milieu, the so called "dysbiosis",
- a bacterial vaginosis and more rarely to
- another infection.

If other infections are suspected, an appropriate examination should be carried out.

The treatment will be performed according to the situation (15). Here are just the most common indications:

- Disturbances of the vaginal milieu without signs of bacterial vaginosis or specific infection: lactobacillus preparations provide the best treatment in these cases.
- If bacterial vaginosis is diagnosed it should be treated either locally or systemically with Metronidazole or Clindamycin.
- Specific infections should be treated accordingly.

Self-care-program

The most important part of our prematurity-prevention-program is the "self-care-program for pregnant patients" which we developed in 1993 as an additional measure (13, 15). Within this self-care-program we recommend that all pregnant patients take an active part, particularly by measuring their own vaginal pH twice a week. They should start as early as possible, at best immediately after pregnancy has been diagnosed.

We recommend to measure the vaginal pH using a CarePlan,VpH-test-glove which we developed in collaboration with the Inverness Medical (Europe) Company; the present distributor is Unipath (Cologne/Germany). The indicator can be compared with a color chart and the pH-value read. If the pH is normal, this means 4.4 or less, the indicator turns yellow. The test-glove packs also contain detailed information about the program for the women. It is also possible to measure the pH with the pH-indicator-strips form Merck Company (Art. No. 1.09542) which have the same indicator field. The strips are cheaper, but do not contain any information which should therefore be supplied.

If the pH is measured twice a week by the patient herself the intervals between measurements are greatly reduced to one eighths compared with the common prenatal care examination once every four weeks by the physician. The apparent chances of very early detection of risk symptoms are substantially superior when the patient measures her pH herself. If a pH-value of 4.7 or more is measured, the pregnant patient is advised to consult her doctor as soon as possible to ascertain the background, and if necessary start treatment.

Other important potential risk factors which can be detected by the patient herself are listed in the information brochure (15). They are advised to get in touch with their doctor immediately if any of these signs are present:

- changes in vaginal discharge,
- burning and itching in the intimate regions,
- signs of urinary tract infection,
- menstruation-like pains etc.
- vaginal bleeding or spotting.

RESULTS

Our results have repeatedly been published (11-14) Just a few results concerning the self-care-program should be mentioned. The self-care-program has been in use since September 1993. The rate of low birthweight infants (<2500g) in those patients taking part in the self-care-program and who had been pregnant before was 6.2%, this means three times less than in immediate previous pregnancies, when it had been 18.3%. It is of special interest to note that the number of very underweight infants (<1500g) was 1.3%, that is six times lower than in the immediate previous pregnancies, when it had been 7.8%. The rate of extremely underweight infants (<1000g) amounted to 0.9%, as opposed to 3.9% previously.

Results from other places: Later Hoyme and cow. (3, 4) achieved similar encouraging results with our program in a prospective project undertaken in Erfurt, the capital of Thuringia, Germany. The excellent results encouraged the Government of Thuringia to employ our program on approval in their whole state. In the second half of the year 2000 the self-care-program was employed and the statistically evaluated results for the entire state were compared with those from the first half of 2000 without the program. The results are impressive and - from our point of view - represent a breakthrough, in as far as most authors dealing with prematurity up to now have stated that in greater population areas the prematurity rate has not

changed at all during the last decades. In Thuringia the results were (5):

- With regard to gestational weeks: the rate of very early born infants with less than 32 gw was 1.58% in the first half of the year 2000, and 0.99% in the second half. This is a significant reduction.
- With regard to birthweight: in infants below 1500g birthweight the rate decreased from 1.29% to 0.97%. In infants with less than 1000g the decrease was significant from 0.61% to 0.38%. This is an even greater decrease.

Conclusion and short critical comment

Currently the self-care-program as has been confirmed by our evaluation and afterwards by two prospective investigations by Hoyme and co. seems to be the most efficient, inexpensive and easily applicable program for prevention of very early prematurity.

But this program is by far not used enough. From our point of view there are a few barriers. In the foreground we see a an iatrogenic barrier, namely a misjudgment of the practical benefit of different strategies for prematurity prevention on a broad scale. From our point of view unfortunately too many of our colleagues concentrate too much on highly sophisticated methods such as ultrasonographic diagnostics, immunobiologic examinations such as cytocines or fetal fibronectin and others. Such diagnostics are of course also important but are mostly concerned with the late stages of the prematurity process and can therefore never be as efficient as our simple, inexpensive and much earlier employed prematurity-prevention program. As far as we know up to now there is no study existing which could convincingly demonstrate that the prematurity rate has been significantly decreased throughout the country only by the use of such methods.

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Global, Regional and National Perinatal and Neonatal Mortality

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ABSTRACT
Globally, the perinatal mortality rate (PMR) is 53/1000 (7.5 million annual perinatal deaths) and the neonatal mortality rate (NMR) is 36/1000 (5.1 million annual neonatal deaths). Of the 141 million annual livebirths, 127 million (90%) are born in developing countries, which, compared to developed countries, have a higher PMR (57/1000 vs 11/1000, 5.2x) and NMR (39/1000 vs 7/1000, 5.6x). Five million annual neonatal deaths (98% of the world's total) occur in developing countries. Regional annual livebirths figures are: Asia-Oceania 76 million, Africa 31 million, Central and South America 12 million, Europe 8 million, and North America 4 million. Regional annual neonatal death figures are: Asia-Oceania 3.3 million, Africa 1.3 million, Central and South America 0.3 million, Europe 0.07 million, North America 0.03 million. The Asia-Oceania region has a PMR of 53/1000 and a NMR of 41/1000. It has half of the world's livebirths and two-thirds of the world's neonatal deaths. The PMR and NMR have often been used as an indicator of the standard of a country's social, educational and healthcare systems. Strategies, which address inequalities both within a country and between countries, are necessary if there is going to be further improvement in global perinatal health.
Key words: Neonatal mortality, perinatal mortality, developing countries

There has been a gradual reduction in global perinatal mortality rate (PMR) and neonatal mortality rate (NMR) over the past decade. Disparities in perinatal health between the five regions (Asia-Oceania, Africa, Central and South America, Europe, and North America) continue to exist, due to differences in their population density and their mix of developed and developing countries. This review examines data on perinatal and neonatal mortality worldwide, makes comparisons between the five world regions, and analyses national differences in the largest of the five regions, Asia-Oceania, which has the greatest number of births as well as neonatal deaths. Data were derived from a variety of sources, including national health service reporting and surveys, and global and regional estimates published by the Maternal Health and Safe Motherhood Programme of the World Health Organization [6].

Global PMR and NMR

At a global level, the PMR is 53 per 1000 births and the NMR is 36 per 1000 livebirths. Perinatal mortality refers to death in the perinatal period that includes late pregnancy, birth and the first week of life. This definition avoids conflicting judgments of whether a fetus exhibits signs of life or not at birth, and is therefore a useful measure of reproductive loss for comparison between countries. Neonatal mortality is defined as the death of a liveborn infant during the neonatal period, which begins with birth and extends to the end of the first four weeks of life. Statistics used for international comparison are generally restricted to neonates weighing 1000 g or more at birth in both the numerator and the denominator. At a global level, there are 7.5 million perinatal deaths and 5.1 million neonatal deaths annually. Two-thirds of neonatal deaths (almost 3.4 million) are early neonatal deaths, that is, they occur within the first week of life.

There are 141 million annual livebirths worldwide. The vast majority of births (127 million or 90%) occur in developing countries. Although the overall PMR of 11 per 1000 and NMR of 7 per 1000 are low in developed countries, only 10% of births (14 million) occur in developed countries. In contrast, the PMR of 57 per 1000 and NMR of 39 per 1000 in developing countries, are 5.2 times and 5.6 times higher than that in developed countries. The consequence is that 5 million deaths or 98% of the

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Table 1. PMR and NMR in the Five World Regions

World Regions	Annual Livebirths	PMR (per 1000)	NMR (per 1000)	Deaths <28d (per year)
Asia-Oceania	76 M*	53	41	3.3 M
Africa	31 M	75	42	1.3 M
Central and South America	12 M	39	25	0.3 M
Europe	8 M	13	8	0.07 M
North America	4 M	9	6	0.03 M

(*=Million)

world's total occur in developing countries, while only 0.1 million deaths or 2% of the world's total occur in developed countries.

Regional PMR and NMR

Regional annual livebirths and neonatal deaths, as well as PMR and NMR, are shown in Table 1. The Asia-Oceania region is the largest of the five world regions. Its 76 million annual livebirths represent 54% of the world's total (Africa 22%, Central and South America 9%, Europe 6%, and North America 3%). Because of its high NMR of 41 per 1000, it has also the highest number of annual neonatal deaths among the five world regions (3.3 million or 66% of the world's total).

PMR and NMR within Asia-Oceania

Of the five sub-regions within the Asia-Oceania region, South Asia has the highest PMR and NMR as well as the highest number of livebirths (Table 2). Its NMR of 51 per 1000 livebirths is the highest of all the geographical regions in the world. The 24 million annual livebirths in South Asia represent 27% of the world's total. Its 2 million neonatal deaths represent a disproportionally high 40% of the world's total.

An examination of the national PMR and NMR of individual countries demonstrates great discrepancies in perinatal health between developed and developing countries. Within the Asia-Oceania region, there are only five countries that have a PMR below 10 per 1000 and a NMR below 5 per 1000: Australia, Hong Kong, Japan, New Zealand and Singapore. However, the numbers of births in these countries with a more favourable PMR and NMR are relatively low: Australia (260,000), Hong Kong (30,000), Japan (1.3 million), New Zealand (60,000)and Singapore (40,000). In total, less than 1.7 million or 2.3% of the annual livebirths in the Asia-Oceania region are born in these five countries. In contrast, countries in South Asia such as Bangladesh, Pakistan, Nepal and India have a PMR of 65-85 per 1000 and a NMR of 50-65 per 1000. Sri Lanka leads the way in South Asia with a PMR of 25 per 1000 and a NMR of 20 per 1000. The countries in East Asia are predominated by China with over 20 million annual livebirths. It has a PMR of 45 per 1000 and a NMR of 35 per 1000. Excluding Hong Kong and Japan, South Korea has the best PMR and NMR in East Asia of 15 per 1000 and 10 per 1000 respectively. Countries in South-East Asia have a relatively wide range of PMR and NMR. The highest is found in Laos and Cambodia and Laos (PMR of 65-90 per 1000 and NMR of 50-70 per 1000), medium high in Indonesia and Myanmar (PMR of 45-55 per 1000 and NMR of 35 per 1000), and medium low in Vietnam, Philippines and Thailand (PMR of 20-25 per 1000 and NMR of 20 per 1000). Excluding the three countries Australia, New Zealand and Singapore, Malaysia has the best PMR and NMR in South-East Asia (20 per 1000 and 10 per 1000 respectively). Countries in West Asia can be divided into three groups. The first group with the highest PMR and NMR includes Yemen, Turkey, Syria and Iraq (PMR of 40-70 per 1000 and NMR of 30-45 per 1000). The second group, which is medium high, includes Iran, Jordan, Oman and Saudi Arabia (PMR of 30 per 1000 and NMR of 20-25 per 1000). The third group, which is medium low, includes Bahrain, Kuwait and United Arab Emirates (PMR of 20 per 1000 and NMR of 15 per 1000).

Table 2. PMR and NMR in the five Asia-Oceania Sub-regions

Asia-Oceania Sub-Regions	PMR (per 1000)	NMR (per 1000)	Annual Livebirths
South Asia	66	51	38 M*
East Asia	41	32	24 M
South-East Asia	37	28	13 M
West Asia	44	27	0.5 M
Oceania	44	24	0.5 M

(*=Million)

Significance of PMR and NMR

The PMR and NMR are useful as an indicator of the standard of a country's educational, social and community health systems, the nutritional status of the population, and the national medical programs in obstetric and neonatal care. Firstly, they reflect the effectiveness of social measures in general and community health action in particular. Secondly, they reflect the quality and availability of obstetric and neonatal healthcare services. Overall, they are a measure of socio-economic development of the country. In developing countries, priority is often rightly given to the reduction of post-neonatal infant mortality and childhood mortality. Therefore, it is not surprising that a reduction in NMR has lagged behind the reduction in infant mortality. The fetus and neonate remain neglected by the healthcare system, and interventions to reduce fetal and neonatal deaths are of a low priority. Nevertheless, effective public health actions and inexpensive clinical interventions can be effective in reducing PMR and NMR that will contribute to an improvement in later infant health. In developing countries with a high NMR, most mortality and morbidity in the neonatal period are caused by conditions that can be prevented or treated. The three main causes of neonatal mortality in developing countries are asphyxia, infection and birth trauma. In most cases, the mortality and morbidity are avoidable. Early detection and management of perinatal sepsis, timely diagnosis and appropriate treatment of antepartum and intrapartum asphyxia, safe and clean delivery, meeting the physiological needs of neonates at birth, and prevention and adequate management of neonatal infections are interventions that are available, attainable and cost-effective. The World Health Organization definition of appropriate technology is one which is scientifically sound but acceptable to users, providers and decision makers, simple in design and execution, that fits with local cultures and can be further developed locally at low cost [3].

Strategies to improve PMR and NMR

A ten-fold difference in PMR and NMR between the developed and developing countries is often associated with a ten-fold difference in healthcare expenditure per capita. For example, among the highest ranking nations in the Asia-Oceania region are Japan ($1760), Australia ($1600), New Zealand ($1390), Korea ($860) and Singapore ($750), while among the lowest ranking nations are China ($74), Pakistan ($71), Indonesia ($56) and Nepal ($41). Nations in between include Thailand ($327), Malaysia ($202), Philippines ($101), India ($84) and Sri Lanka ($77). Furthermore, in many developing countries, there is maldistribution of healthcare resources in that a great proportion of the limited budget that are spend in the provision of healthcare reaches only the more privileged members of the community. It is not uncommon to find that 80% of the country's doctors are serving 20% of the population residing in the urban areas. Conversely, only 20% of resources are available to 80% of the population who are residing in rural areas. Even in countries where there is an improving economic condition overall, the gap between rich urban areas and poor rural areas is widening. This is observed in both developed countries and developing countries alike [1, 2].

Strategies that address inequalities within a nation and between nations are necessary if there is going to be a further improvement in global perinatal health in the present century. Currently, developed countries often give less than 0.5% of their Gross National Product (GNP) to developing countries. A target for the governments of affluent nations facing up to their global responsibilities is to contribute at least 1% of their GNP to developing countries. A tension exists between the provision of what is regarded as good healthcare to all and freedom of personal choice. Alterations in traditional cultural practices, habits of hygiene, and family size, cannot be rushed and coercion is often required. Several developing countries that have succeeded in making real progress in reducing their PMR and NMR have less personal freedom in birth control measures than those living in developed countries would find acceptable. Each individual's interests are seen as subordinate to the interests of the whole society or country [4]. The obstetrician and neonatologist must often take into account more than the health of the mother and infant and the values and happiness of the parents, when making critical clinical decisions in the course of their care of the mother and neonate.

Conclusions

Compared to perinatal data from 1983 [5], global PMR has reduced by about 10% in just over one decade. However, the total number of perinatal deaths has remained unchanged, because the number of births had increased. A 35% reduction in PMR has been observed in developed countries (from 17 per 1000 to 11 per 1000), whereas developing countries saw only an 11%

reduction in PMR (from 64 per 1000 to 57 per 1000). The largest world region, Asia-Oceania, only experienced a 7% reduction (from 61 per 1000 to 53 per 1000) over the same period. Preventive interventions in developing countries directed against perinatal asphyxia, infections and trauma, are simple and cost effective. In order to see a significant reduction in global PMR and NMR over the coming decade, it is important for the international community to make a greater effort to support developing countries that wish to improve healthcare delivery to mothers and infants.

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Fetal Weight Estimation in Diabetic Pregnancies and Suspected Fetal Macrosomia: The Real Facts

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Pregnancy is often complicated by diabetes, either preexisting or diagnosed during gestation. The reported prevalence of gestational diabetes mellitus (GDM) is 3% to 5% of all live births [1], and even higher in selected populations, such as Mexican-Americans, Asians, and Indians [2,3]. Clinicians have witnessed a significant improvement in outcome of diabetic pregnancies owing to improved perinatal maternal glycemic control, close antepartum surveillance, and advances in neonatal care, although the risk of fetal macrosomia and adverse perinatal outcome has not been eliminated.

Ultrasound is an important tool for monitoring diabetic pregnancies. It is used to assess gestational age, congenital anomalies, fetal well-being (dynamic assessment), and growth abnormalities such as macrosomia and fetal growth restriction. However, the role of fetal weight estimation by ultrasound in predicting adverse perinatal outcome remains controversial. The failure to correctly estimate fetal weight has important clinical implications and has been incorporated in litigations involving complicated deliveries, which in rare cases can result in persistent brachial plexus injury.

This paper reviews the literature on the accuracy of ultrasound in estimating fetal weight in diabetic pregnancies. We focused specifically on its role in the prediction and clinical management of fetal macrosomia.

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Macrosomia

Excessive fetal growth is defined in two ways. Infants large for gestational age (LGA) have a birth weight equal to or greater than the 90th percentile for their gestational age. This factor, however, varies according to the specific population under study. In the United States, for example, a recent national survey reported that fetal weight in the 90th percentile at 37, 40, and 42 weeks of gestation is 3,755, 4,060, and 4,098 gr, respectively [4]. Fetal macrosomia is defined as growth beyond a specific weight, usually 4,000 or 4,500 gr, regardless of gestational age. The risk of morbidity in infants and mothers when the birth weight is between 4,000 and 4,500 gr is greater than that in the general obstetric population, and it increases sharply beyond 4,500 gr. This cutoff is supported by recent large cohort studies [5].

Ten percent of all live-born infants in the United States weigh more than 4,000 gr, and 1.5% weigh more than 4,500 gr [1]. Both gestational and pregestational diabetes are associated with fetal macrosomia. In one study, 6% of mothers with untreated borderline GDM delivered infants weighing more than 4,500 gr, compared with only 2% of women with normal glucose tolerance [6]. If full-blown GDM is unrecognized and untreated, the risk of macrosomia may be as high as 20% [7].

Shoulder dystocia

Shoulder dystocia is the most serious complication of fetal macrosomia; the risk is 1.4% for all vaginal deliveries [8], and it rises dramatically to 9.2% - 24% when the birth weight exceeds 4,500 gr [9, 10]. In diabetic pregnancies, birth weights greater than 4,500 gr have been associated with 19.9% to

50% rates of shoulder dystocia [9, 10]. Shoulder dystocia may also be associated with other birth traumas, such as Erb's palsy, clavicular fracture, fetal distress, low Apgar score, and birth asphyxia [11], although 25 to 75% of brachial plexus injuries are unrelated to antecedent shoulder dystocia [12].

Macrosomia due to maternal diabetes is different from macrosomia due to other predisposing factors [13, 14]. Macrosomic infants of diabetic mothers tend to have greater total body fat, greater shoulder and upper-extremity circumferences, greater upper-extremity skin-fold measurements, and smaller head-to-abdominal-circumference ratios than macrosomic infants of nondiabetic mothers. This may explain the higher incidence of shoulder dystocia in these infants [14].

Ideally, clinicians should diagnose macrosomia in the antenatal period so that they can offer the optimal mode of delivery for preventing shoulder dystocia on the one hand, and sparing unnecessary cesarean sections on the other.

Ultrasonographic diagnosis of fetal macrosomia

The diagnosis of fetal macrosomia has been the subject of much clinical concern and scientific investigation. Over the past 30 years, investigators have introduced formulas based on sonographic measurements of fetal organs to estimate fetal weight. The older formulas used the fetal head, abdomen, and femur, either alone [15] or in combination [16, 17]. Some authors demonstrated differences in accuracy and precision among these formulas [18, 19]. Regardless of the formula used, the accuracy of the fetal weight estimation decreased with increasing birth weight [20-22]. For example, Hadlock's formula has a mean absolute percent error of 13% for infants weighing more than 4,500 gr but only 8% for nonmacrosomic infants [23]. Others showed that in women without diabetes, ultrasound biometry used to detect macrosomia has a sensitivity of 22–44%, specificity of 99%, positive predictive value of 30–44%, and negative predictive value of 97–99% [18, 24]. In addition, the error rates of the regression functions that generate the sonographic estimates of fetal weight are similar to the error rates of the clinical estimates [25]. Ultrasonographic fetal weight estimation at the 90th percentile or above has a sensitivity range of 6.7-89%, and a specificity range of 62-98%. The same calculation for birth weight of 4,000 gr or more has a sensitivity range of 11-100% and a specificity range of 48-100% [25]. O'Reilly-Green and Divon [24] and Miller et al. [26] found that the optimal cutoff for sonographic fetal weight estimation in predicting a birth weight of ≥4,000 gr is 3,700 gr. The prediction of macrosomia in fetuses in breech presentation is more difficult than in fetuses in cephalic presentation [27]. The reported mean absolute percent error for breech and cephalic presentations are 12.9% and 9.5%, respectively.

To overcome these drawbacks, alternative sonographic markers for fetal macrosomia have been proposed which take advantage of the presumed correlation between subcutaneous fat deposition and fetal weight. Three-dimensional ultrasound measurements of fetal upper arm volume [28, 29], fetal chest [30], abdominal [31] and humeral [32] soft tissue thickness, and cheek-to-cheek diameter [33], as well as of the subcutaneous tissue/femur length ratio [34, 35], are associated with varying efficacies. Sacks and Chen [36] reviewed population-based studies of the clinical performance of ultrasound in predicting macrosomia. They concluded that only 15 to 81% of babies (median 67%) predicted to be macrosomic are indeed macrosomic at birth, and that 50 to 100% (median 62%) of all cases of macrosomia are successfully predicted by sonographic measurements. Therefore, like with clinical estimates of fetal weight, the true value of ultrasonography in the management of fetal macrosomia may be its ability to rule out the diagnosis (negative predictive value) [5]. This is especially important given the fact that clinicians who suspected fetal macrosomia on the basis of an ultrasonogram were more likely to diagnose labor abnormalities and were more likely to perform cesarean deliveries despite normal birth weights [37].

Individualized fetal growth estimation curves, such as the complex mathematical model of Rossavik, have not proven more accurate. The prediction error of Rossavik's model averaged 6.1% and ranged from 3.6% to16.5% [25]. By contrast, serial measurement of the abdominal circumference (AC) had a sensitivity and specificity of 84% and 100%, respectively, in predicting birth weight in the 90th percentile or above [38]. For single measurement the sensitivity and specificity were 54% and 89%, respectively. A single measurement of abdominal circumference above the 90th percentile has a relative risk of only 5.5 for birth weight in the 90th percentile or above, whereas serial measurements have a relative risk of 32 [25].

Other techniques for estimating fetal weight have been reported as well, such as magnetic resonance imaging, which yielded estimates within 3% of the actual birth weight in 11 patients with babies weighing 1,600 – 3,300 gr. This compared favo-

rably with the 6.5% error by sonographic examination of the same patients [39].

Prediction of macrosomia in diabetic pregnancies

The estimation of fetal weight in diabetic pregnancies involves special considerations. Because of the disproportionate contribution of fat to fetal body weight and the lower density of fat compared to lean body tissue, equations derived from cross-sectional data may theoretically overestimate the fetal weight when applied to the GDM population [40]. Furthermore, the time from examination to delivery may influence the accuracy and precision of the sonographic estimates [24, 41, 42].

Currently, no single sonographic measurement is capable of distinguishing between LGA and appropriate-for gestational-age (AGA) infants in diabetic pregnancies. Although the finding of an abdominal circumference above the 90th percentile in the second or third trimester is positively associated with fetal macrosomia, the actual birth weights of the babies predicted to be macrosomic on this basis overlap with those of AGA babies in a substantial proportion of cases [43].

Clinical studies have found no significant differences in absolute percent error of birth weight between infants of women with and without diabetes [23]. The accuracy of birth weight prediction by ultrasound and by clinical estimates has been analyzed in a number of studies [44-49]. When the sample was limited to babies with an actual birth weight of >4,000 gr, no significant differences were found between the clinical and ultrasound estimates at or near the onset of labor. The sensitivity of the sonographic estimates in predicting birth weight at the 90th percentile or above in diabetic pregnancies ranged from 70-96%, and specificity ranged from 77-100% [25]. Corresponding values for predicting a birth weight of ≥ 4,000 gr were 33-69% and 77-98%.

Other measurements did not prove superior in diabetic pregnancies [25]. These included the femur length/ abdominal circumference ratio, the abdominal diameter/ femur length ratio, the chest/ biparietal diameter ratio, and soft tissue thickness. Cohen et al [50], in a study of the value of the difference between the abdominal and biparietal diameters in predicting shoulder dystocia in diabetic pregnancies, found that the cutoff value of ≥2.6 cm had a sensitivity of 100% and a specificity of 56%.

Hendrix et al [51] reported that when birth weight was 4,000 gr or more, the absolute error of the clinical estimates was 5.3% and of the sonographic estimates, 13%. Ninety-two percent of the clinical estimates were within 10% of the birth weight compared with 33% of the sonographic estimates. McLaren et al. [52] showed that the 90% prediction limits for an estimated fetal weight of 4,000 gr in diabetic pregnancies included birth weights from 3,410 to 4,675 gr. When the birth weight exceeded 4,500 gr, only 50% of the fetuses actually weighed within 10% of the ultrasound-derived estimate [53].

Role of ultrasound in the management of diabetic pregnancy

Glucose intolerance and fetal abdominal circumference

Parretti et al. [54] recently showed that fetal abdominal circumference, which is considered as a parameter of growth of insulin-sensitive tissues, is influenced by postprandial glucose peaks even in nondiabetic pregnancies. They examined the correlations between maternal glucose levels and sonographic parameters of fetal growth in a longitudinal study of 51 Caucasian nonobese pregnant women with normal glucose challenge tests. Results showed that concomitant with a slight but progressive increase in daily mean glucose levels from 28 weeks (71.9 ± 5.7 mg/dl) to 38 weeks (78.3 ± 5.4 mg/dl), demonstrating the known deterioration of glucose tolerance during the course of normal pregnancy, there was a significant positive correlation at 28 and 36 weeks of gestation between postprandial glucose values and fetal abdominal circumference, and a negative correlation between head-abdominal circumference ratio and 1-h postprandial blood glucose values.

These findings are in agreement with those of diabetic pregnancies, in which a 1-h postprandial maternal blood glucose concentration in the third trimester is considered a strong predictor of infant birth weight and fetal macrosomia [55]. Furthermore, in diabetic pregnancies, fetal hyperinsulinism and birth weight have been found to correlate best with 1-h postprandial glucose values [56]

Insulin treatment

Buchanan et al. [57] suggested that insulin may treat early macrosomia diagnosed in ultrasound. They randomized 98 women at 29-33 weeks' gestation with a fetal abdominal circumference exceeding the 75th percentile for gestational age to either diet therapy alone or diet therapy with twice-daily insulin. They found that the addition of insulin decreased the likelihood of birth weight greater than the 90th percentile from 45% among those treated with diet only to 13% among those rece-

iving insulin.

Recently, the same group of investigators [58] compared management based on maternal glycemic criteria with management based also on fetal abdominal circumference measurements in order to select patients for insulin treatment of GDM. Ninety-eight women with GDM and fasting hyperglycemia were randomized to two groups: insulin treatment or insulin treatment only if abdominal circumference was at the 70th percentile or greater and/or if any venous fasting plasma glucose measurement was >120 mg/dl. The authors found no between-group differences in birth weight, frequency of birth weight above the 90th percentile (6.3% vs 8.3%), or neonatal morbidity. Thus, in women with GDM and fasting hyperglycemia, measurements of glucose plus fetal abdominal circumference identified pregnancies at low risk of macrosomia and sparing in 38% of the patients of insulin therapy with no increase in neonatal morbidity.

Fetal weight estimation and prophylactic cesarean delivery

Macrosomia is distinctly more common in women with GDM, and shoulder dystocia is more likely at a given birth weight in pregnancies complicated by diabetes than in nondiabetic pregnancies. Therefore, it may be reasonable, to recommend cesarean delivery without a trial of labor at some particular threshold of fetal weight. However, the clinical effectiveness of this practice has not yet been established [5]. According to one observational study in which 1,337 women with diabetes were offered either elective cesarean delivery if the ultrasound-derived fetal weight estimate was beyond 4,250 gr or induction of labor if the ultrasound predicted an LGA infant but weighing less than 4,250 gr [59]. Findings were compared with a historic control group of 1,227 women with diabetes. Results yielded a nonsignificant reduction in the risk of shoulder dystocia from 2.4% in controls to 1.1% in the intervention group, and a significant increase in cesarean delivery rate from 21.7% in controls to 25.1% in the intervention group.

In two additional reports analyzing the policy of prophylactic cesarean delivery for macrosomia, which took into account the reported sensitivity and specificity of ultrasonography, the authors calculated that 3,695 cesarean deliveries would be required to prevent one permanent injury, at a cost of $8.7 million for each injury avoided [60,61]. For pregnancies complicated by diabetes, these figures were still high at 443 cesarean deliveries to prevent a single permanent injury.

On the basis of these findings, the American College of Obstetricians and Gynecologists [5] stated that, "Because of the lack of well-designed and well-executed randomized clinical trials, a policy of prophylactic cesarean delivery for suspected fetal macrosomia less than 5,000 g may not be effective for pregnancies without diabetes. Furthermore, even for pregnancies complicated by diabetes, the cost-effectiveness of such a policy is doubtful." They concluded that, "Although the diagnosis of fetal macrosomia is imprecise, prophylactic cesarean delivery may be considered for suspected fetal macrosomia with estimated fetal weights greater than 5,000 g in women without diabetes and greater than 4,500 g in women with diabetes". However, these conclusions were modified in their latest Practice Bulletin [62], which suggested that, "Because of the higher likelihood of shoulder dystocia at a given birth weight in the pregnancies of women with diabetes, it may be best to apply the above recommendation to an estimated fetal weight greater than 4,000 g for GDM. Operative deliveries from the midpelvis should be avoided, if possible, in patients with GDM who have an estimated fetal weight of 4,000 g or more and a prolonged second stage of labor "

Summary

Ultrasound is a useful predictor of macrosomia from a statistical point of view [25], but it has limited applications in clinical practice because of its substantial false-positive and false-negative rates [25]. Serial sonographic measurements can increase the positive predictive value. One study suggested that sonographic laboratories might improve their results by performing receiver operator characteristics (ROC) curve analysis on their own data, in order to select a better cutoff value to predict macrosomia [25].

On the basis of the data collected so far, several key statements can be made regarding the accuracy of ultrasound in predicting fetal macrosomia:

1. Regardless of the formula used, the accuracy of the EFW decreases with increasing birth weight.

2. A disparity in ultrasound measurements between by different operators in individual subjects should be taken into account.

3. Formulas incorporating measurements of the fetal head are of less clinical value for patients in labor.

4. The time elapsed between the fetal weight estimation and delivery may influence the accuracy and precision of the estimate.

5. Although variations in either maternal obesity or amniotic fluid index alone do not significantly influence predictive accuracy, the combination of maternal obesity, anterior placentation and oligohydramnios may eliminate the possibility of accurately measuring fetal parts.

6. The diagnosis of fetal macrosomia is imprecise. For suspected fetal macrosomia, the EFW using ultrasound biometry is believed to be no more accurate than the EFW obtained by clinical palpation [5, 49]. However, a recent prospective study showed that the accuracy of ultrasound estimation of fetal weight was better than maternal and clinical estimation of fetal weight [63].

7. To date, non of the management algorithms developed for selective interventions that are based on the sonographic EFW have demonstrated any efficacy in reducing the incidence of either shoulder dystocia or brachial plexus injury.

Should ultrasound be used to identify fetal macrosomia in low-risk pregnancies or in pregnancies complicated by diabetes? It is clear that ultrasound-derived fetal weight estimates alone are not sufficient grounds for deciding the route of delivery [5, 64]. To asses the risk of macrosomia in both diabetic and nondiabetic pregnancies, other known risk factors should also be taken into account, such as prior history of macrosomia, maternal pre-pregnancy weight, weight gain during pregnancy, multiparity, fetal sex (male), gestational age (>40 weeks), ethnicity, maternal birth weight, and maternal height [5]. To determine the mode of delivery, the clinical fetal weight estimate, subjective maternal weight estimate, and clinical pelvimetry findings should be added to the sonographic fetal weight estimate (preferably by serial measurements which include the abdominal circumference), with consideration of the above risk factors for macrosomia. Furthermore, as suggested recently [65], the use of additional examiners to perform the sonographic estimates may reduce the absolute weight difference, especially with repeated measurements of abdominal circumference.

In the future, three-dimensional ultrasound and magnetic resonance imaging are expected to generate better ROC curves than those of two-dimensional ultrasound or clinical estimates [25].

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Exogenous Surfactant in the Neonate

Suggestions for its use in developing countries

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In spite of improvement in perinatal assistance, the frequency of Respiratory Distress Syndrome in preterm babies (NRDS) remains very high.

The estimated incidence of NRDS in babies with a birth weight of 500- 750 g (very low birth weight -VLBW-) reaches a value of over 80% and in babies with a birth weight between 1000 and 1500 g the frequency is over the 30% (1). Survival significantly improved with the introduction of new techniques of prevention and of treatment of the disease, in particular, after the introduction of the exogenous surfactant.

In the United States of America (USA), the neonatal mortality related to NRDS declined by 28% between 1988 and 1991; this data was temporally associated with widespread use of surfactant therapy and was the single most important factor for the reduction in overall neonatal mortality in the US. (1)

Now, the exogenous surfactant is in widespread use in many countries, however, there is great variability in its use, within and among countries, related not only to different medical strategies and organisations, but also to the costs. The surfactant preparations currently on the market are relatively expensive and their supply is relatively limited. Therefore an accurate planning of the indications is necessary.

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Prevention of NRDS

Two main strategies are available for the prevention of NRDS (prophylaxis):

-one is antenatal (before-birth) with the administration of corticosteroids to mothers, at risk of preterm delivery, thus accelerating fetal lung maturation and

-one is after birth, by giving in the delivery room, as soon as possible, exogenous surfactant to the new-borns.

Antenatal prophylaxis

The antenatal corticosteroid treatment for prophilaxis of NRDS proposed by Liggins and Howie in 1972 is effective in reducing the frequency and the severity of the disease(2).

Moreover, use of steroids during the perinatal period affects almost all body systems, enhancing cell differentiation but reducing cell division.

Some negative side effects on growth, development and circulation have been described in animals and in humans. The most evident acute adverse effects on the fetus are: reduction of the fetal body and breathing movements, reduction in fetal heart rate variability. Other severe adverse effects reported are: fetal and placenta growth retardation, disturbances of growth and functional differentiation of the central nervous system, increase of pre-term delivery, increased susceptibility to infections, depression of adrenal function (low cortisol level in new-borns), and transient hypertrophic cardiomyopathy. The most

important long term adverse effects are related to the neurological system with abnormal neurological development, cerebral palsy and they suggest a warning against indiscriminate use of steroids during fetal life.

The prenatal prophilaxis of the NRDS with steroids presents important advantages such as; easy administration, very low costs, reduction in the need of intensive care, reduction in mortality and morbidity, therefore, a single course of corticosteroids is recommended for mothers at risk of preterm delivery and who are between 24 and 34 weeks gestation(3).

Repeated antenatal courses must be avoided, they may have lasting negative side effects on fetal grow and neurological development without clear benefits for the fetus. (4)

Betamethasone has more pronounced side effects but also more beneficial effects than dexamethasone, therefore, it is the drug of choice.

The main scheme for prenatal prophilaxis foresees the administration of betamethasone at the dose of 12 mg repeated after 12 or 24 hrs (5).

Postnatal prophylaxis

A new way to prevent NRDS is the administration of exogenous surfactant to the newborn at birth, as soon as possible, in the delivery room.

Some experimental data suggest that it would be better to give the surfactant immediately after birth (6,7).

In fact, in surfactant deficient infants the leak of serum proteins into the alveoli inhibits the endogenous surfactant, moreover, surfactant deficient animals present necrosis and desquamation of bronchiolar epithelium already within a few minutes after the onset of ventilation.

Recently, Werner and Bjorklund demonstrated that in immature new-born animals the mechanical ventilation, also for a brief period, damages the lungs with a reduction of respiratory compliance that remains permanently lower than in the controls, also after surfactant administration (8).

In 1996, to evaluate the effects of an early administration of exogenous surfactant in the delivery room (prophylaxis), to prevent NRDS, we performed a multicenter randomised clinical trial using a natural porcine exogenous surfactant (Curosurf) (9)

Before-birth babies with gestational ages between 24 and 30 weeks, were randomised (stratified in three groups on the basis of the gestational age) for prophilaxis or as controls.

In all the babies the rescue treatment was allowed in the cases of NRDS with need of mechanical ventilation.

We enrolled a total of 268 cases, 136 in the group of prophilaxis and 132 as controls.

The two groups were comparable in clinical characteristics.

In the group with prophylaxis mortality, grade III or IV NRDS and need of rescue treatment with surfactant were significantly lower than in the control group.

We observed, also, a reduction of other unfavourable clinical outcomes such as IVH, pneumotorax, interstitial emphysema and pneumonia, but the differences were not significative.

Combined unfavourable outcomes of mortality + BPD and mortality + BPD+IVH

Table 1. Main Factors Predisposing an Infant to RDS

1. Prematurity. Incidence of RDS increase with the decrease of gestational age (g.e.). Over 80% in infants with g.e. under 28 wks.
2. Male sex. Boys are more likely than girls to suffer from RDS and have a higher mortality.
3. Ethnic origin. RDS is more common in white than in non-white neonates.
4. Perinatal asphyxia. Increase the risk for RDS in both the term and preterm population.
5. Maternal Diabetes. Insulin delays the maturation of alveolar Type II cells.
6. Multiple pregnancies. Mainly related to low gestational age.
7. Caesarean section. Mainly related to low gestational age.
8. Familial disposition. If a women has one baby with RDS the risk in subsequent pregnancies increase. Surfactant protein B deficiency is an autosomal recessive condition, which presents as severe and persistent RDS, resulting in death.
9. Antenatal corticosteroids. The administration of corticosteroids to a mother who subsequently delivers a preterm baby, reduce the risk of developing RDS and mortality.

These factors are considered indicators of the need for prophylactic surfactant.

and retinopathy of the prematurity (ROP) were also significantly lower in prophilaxis than in the control group.

The prophylaxis with surfactant in the delivery room is more effective than rescue treatment and it "saves about seven more lives than rescue treatment for every one hundred babies treated".(10-14)

The prophylaxis, however, increases the number of unnecessary treatments. A percentage of babies, ranging from 20% to 40 %, depending on the gestational age, will receive the treatment without need because they never should have developed NRDS. This means an increase in surfactant's consumption and costs.

With regards to the problem of costs, Morley estimated that "prophylactic surfactant would cost about seven more doses of surfactant for every extra life saved."(10)

All these advantages and disadvantages must be taken into account, in particular, with planning of neonatal assistance in the developing countries.

A suggestion may be to reserve the prophilaxis for the babies with gestational ages between 26 and 28 weeks and for babies with gestational ages over 28 wks. that require intubation for management or for resuscitation in the delivery room.

Moreover, there are some predisposing factors that can help to choose prophylaxis or rescue treatment (Tab. 1).

In extremely low gestational new-born ages (<26 wk.) the surfactant administration, as prophylaxis or as rescue treatment, must be evaluated case by case and discussed with the parents, because of the poor outcomes of these babies.

In our study on prophylaxis in the delivery room with exogenous surfactant, considering the three different subgroups stratified at randomisation on the basis of the gestational age, we observed that prophilaxis reduces severe NRDS in the same way in the different gestational ages, but the mortality is only slightly reduced in the lower gestational ages. These babies, probably, suffer from other problems than lung immaturity.

The prophylaxis is more effective than rescue treatment but it is necessary to consider, additionally, the cost and the availability of exogenous surfactant preparations for each country before recommending it for the prevention of NRDS. The surfactant preparations currently on the market are relatively expensive and the supply is relatively limited.

A low dose of surfactant for prophylaxis of NRDS should be sufficient (15)

Rescue treatment

Exogenous surfactant is the drug of choice for the treatment of established NRDS.

Surfactant replacement therapy improves lung function, reduces mortality and incidence of air-leak complications.

These beneficial effects have been obtained with human surfactant isolated from amniotic fluid, modified natural surfactant of bovine or of porcine origin, as well as with protein free synthetic surfactant, although natural surfactants are more effective than artificial ones. (14, 15-17)

To evaluate the efficacy of surfactant treatment of severe NRDS, in 1988, we performed a randomised multicenter trial, involving the collaboration of eight European neonatal intensive care: 146 patients with a mean gestational age of 28.4 to 28.8 wks. and a mean birth weight of 1246 to 1182 g were enrolled. 77 babies received a large single dose (200 mg/ kg) of a natural porcine surfactant preparation (Curosurf) and 69 infants, that resulted at randomisation as controls, received the same assistance as the treated babies with the exception that no surfactant was instilled into the air-ways (16).

Babies receiving surfactant showed, within a few minutes, a dramatic improvement of oxygenation as reflected by a near threefold increase of the PaO_2/FiO_2 ratio, neonatal mortality (28 days) decreased from 51% to 31% (P<. 05), incidence of pulmonary interstitial emphysema (23% v 39% P<. 05) and pneumothorax (18% v 35% P<. 05)

Many other randomised clinical trials have definitively demonstrated the efficacy of surfactant treatment of NRDS, however, the best timing of surfactant administration, in clinical practice, has not yet been clearly established (14). The early administration offers the advantage in

that the disease is less severe, however, there exists varying percentages of unnecessary treatment and of surfactant consumption similarly as in prophilaxis (9,11).

To evaluate the effects of a precocious treatment with exogenous surfactant of babies with NRDS we performed, in 1993 (in 8 different states in Europe), a multicenter randomised trial involving a total of 182 new-borns with NRDS and needing mechanical ventilation with an FiO_2 between 0,40 and 0,59.

The new-borns of the "early treatment" group received, immediately after randomisation, a single dose (200 mg /Kg bw) of a natural porcine surfactant (Curosurf), while in the control group the treatment was reserved for those babies who needed mechanical ventilation with a FiO_2 above 0.60.

The babies enrolled were comparable with regards to clinical characteristics, in particular, regarding gestational ages and birth weights(18).

The most impressive effects of the precocious treatment was a significant reduction in mortality, in IVH grade III or IV and death + BPD.

The duration of oxygen therapy and of IPPV was also reduced (in the babies with early treatment).

On the basis of these results we concluded that early treatment is better than the delayed one and it is recommended for babies with lower gestational ages.

Similarly, an early treatment with exogenous surfactant of pre-term infants (<30 wk. gestational age) receiving nasal continuous positive airway pressure (CPAP) reduces mortality and the need of mechanical ventilation (19).

Conclusions

In summary, the suggestions for the developing countries should be:

- Prenatal prevention of NRDS with a single course of corticosteroids for mothers at risk of a pre-term delivery and that are between 24 and 34 week's gestation must be recommended. Repeated antenatal courses must be avoided.

- Postnatal prophilaxis with exogenous surfactant can be reserved for babies with gestational ages between 26 and 28 weeks with evidence of high risk for NRDS (male sex, perinatal asphyxia, need of intubation at birth, incomplete course of antenatal corticosteroids, caesarean section, multiple pregnancies, maternal diabetes) and for babies with gestational ages over 28 wks. that require intubation.

- For prophylaxis a low dose of surfactant can be used.

Rescue treatment with exogenous surfactant is recommended for new-borns with gestational ages between 26-28 wks. with clinical evidence of NRDS. The early administration of a single low dose of surfactant improves the outcomes and the results are more effective than delayed treatment and, therefore, it is recommended.

- The rescue treatment of new-borns with NRDS who need intermittent positive pressure ventilation (IPPV) with a FiO_2 > 40%, is mandatory.

- The replacement therapy of established NRDS, should be initiated as soon as possible even only on the basis of a clinical diagnosis.

- In new-borns with gestational ages > 28 weeks with NRDS, treatment may be delayed to reduce the number of unnecessary administrations and reserved for babies that need intermittent positive pressure ventilation (IPPV). In these cases the full dosage of the available surfactant is mandatory.

- In new-borns with extremely low gestational ages (<26 wk.) the surfactant administration must be evaluated case by case and discussed with the parents because of the poor outcomes of these babies.

- Surfactant administration, after a brief intubation, in the spontaneously breathing babies treated with CPAP might be useful to avoid mechanical ventilation

- Surfactant must be administered by qualified physicians trained in neonatal intensive care and in management of mechanical ventilation of VLBW infants.

- Supplementary surfactant should be used routinely only in institutions having all the necessary facilities for the management of VLBW infants and for mechanical ventilation.

- In some circumstances, the surfactant administration should be done in periphe-

ral hospitals, to WLBW infants waiting to be transferred to a NICU.

A clinical study we conducted in Rumania in 1996, at a time when neonatal respirators and NICUs too, were not available in that country- showed an improvement of clinical and respiratory conditions in new-borns with a mean gestational age of 30 wks, receiving surfactant supplementation in the first minutes of life with respect to the control group (20).

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Postresuscitative Management of Asphyxiated Term/Preterm Infant

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In spite of successful resuscitation of an asphyxiated infant, hypoxic-ischemic encephalopathy (HIE) develops in the setting of perinatal asphyxia, which is a multiorgan system disease. Previously it was reported that involvement of one or more organs occurred in 82% of the infants; the central nervous system (CNS) was most frequently involved (72%). Severe CNS injury always occurred with involvement of other organs. Renal involvement occurred in 42%, pulmonary in 26%, cardiac in 29% and gastrointestinal in 29% of the infants (1).

Postresuscitative management of the asphyxiated infant can be divided into two categories. The first one is the general supportive care in which clinical management is directed at maintenance of adequate ventilation, cerebrovascular perfusion and adequate blood glucose levels. This therapeutic approach is necessary for the organs to regain their baseline functions. The second one is neuroprotective therapy, which should be planned according to the phase of postasphyxial injury.

General supportive care of asphyxiated infant:

Physical examination:

Physical examination of the asphyxiated infant is important for evaluation and predicting outcome. Level of consciousness (LOC), respiratory pattern, brain stem function and motor exam are correlated with the severity of asphyxial insult (2). It is better to evaluate these features periodically because they can change by time. Sarnat & Sarnat created a scoring system to evaluate the degree of asphyxia (3). (Table 1)

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Monitoring the infant:

Assessment of the newborn's oxygen status includes evaluation of cyanosis, pulse-oximeter monitoring and blood acid-base assessment. With careful oxygen monitoring, significant periods of hyperoxia and desaturations can be avoided.

Capillary refill, color, metabolic acidosis, and heart rate can assess peripheral perfusion. Arterial blood pressure monitoring can be obtained intermittently with a non-invasive doppler device or continuously with an indwelling catheter. Acute episodes of severe hypotension during resuscitation can be managed by giving 10 cc/kg of volume over 10-15 minutes as fresh frozen plasma (FFP) or normal saline (4). In the majority of preterm infants, especially during the immediate postnatal period, hypotension is primarily caused by abnormal peripheral vasoregulation and/or myocardial dysfunction and not by absolute hypovolemia (5). For this reason aggressive volume overload can be harmful. Volume support should be limited to 10-20 ml/kg isotonic saline and if hypotension persists, early initiation of dopamine is required. Both dexamethasone and hydrocortisone in preterm infants improved hypotension, which was resistant to volume load and vasopressors (6,7). Sudden increase in blood pressure lead to capillary disruption and intracranial hemorrhage.

Elevated levels of plasma CO_2 have two effects on the central nervous system. First, increased serum CO_2 concentrations will increase tissue CO_2 levels and worsen intracellular acidosis. Second, elevated levels of CO_2 cause vasodilatation, which increase the risk for hemorrhage. Hypocarbia should be avoided as well. Decreased serum CO_2 causes vasoconstriction that worsens the cerebral blood flow (8). Transcutaneous devices can be as sensitive as 82% and specific as 94% in detecting hypocarbia and 90% and 94% for hypercarbia, respectively (9).

Table 1. Clinical Features of Hypoxic-ischemic Encephalopathy

Stage 1	Stage 2	Stage 3
Hyperalert	Lethargic or obtunded	Stuporous, responds to strong stimuli only
Normal muscle tone	Mild hypotonia	Flaccid
Weak suck	Weak or absent suck	Intermittent decebration
Low threshold Moro	Weak Moro	Absent suck
Mydriasis	Miosis	Absent Moro
No seizures	Focal or multifocal seizures	Poor pupillary light response

As a summary the aim of monitoring is to maintain adequate oxygenation and perfusion with normalization of blood pressure, and avoidance from hypercarbia and hypocarbia. Management of the infant can be individualized according to the priority of the involved organs.

Cardiovascular

Hypotension, tachycardia, poor perfusion, decreased pulses and congestive heart failure may follow severe perinatal asphyxia (10). These signs are often associated with respiratory distress. These cardiovascular effects have been referred to as hypoxic myocardiopathy or cardiogenic shock. Electrocardiogram shows myocardial ischemia and echocardiogram shows reduced contractility, and provide information about pulmonary hypertension.

Early and adequate ventilation with correction of hypoxemia, acidosis and hypoglycemia are essential. Management of cardiac injury includes the use of inotropic agents to increase myocardial contractility and cardiac output. The combination of low dose dopamine with dobutamine is an effective treatment for cardiac failure secondary to asphyxia (5,11). Hunt and Osborn (12) concluded that current data about the use of dopamine for the prevention of mortality or improvement long-term neurodevelopmental outcome in term newborn infants with suspected perinatal asphyxia was insufficient. Epinephrine should be avoided if possible because of resultant significant vasoconstriction that can worsen peripheral perfusion and contribute to metabolic acidosis. It was stated that persistently low cardiac output predicts high mortality in newborns with cardiogenic shock (13). A child with abnormal rhythms reflects the loss of central control of heart rate and carries a bad prognosis.

Pulmonary

These neonates are at risk for meconium aspiration syndrome, respiratory distress syndrome, persistent pulmonary hypertension (PPHN), pulmonary hemorrhage and pulmonary edema (14). Pulmonary involvement exhibits a wide spectrum of clinical picture changing from minimal oxygen requirement to persistent pulmonary hypertension. Hypoxia induces pulmonary vasoconstriction and pulmonary vascular resistance increases. Intrapulmonary shunts as well as right-to-left shunting across ductus arteriosus occurs (15). Echocardiogram features of the PPHN are tricuspid regurgitation, increased right ventricle pressure and right-to-left shunting. If the conventional treatment fails, PPHN should be treated with NO and ECMO (16). Alveolar lining damage and increased alveolar permeability leads to plasma and red cell effusion and fibrin deposition. As a result surfactant production is decreased. It is defined as Shock Lung (8). Treatment approach is supportive with oxygen supplementation, adequate ventilation. The role of Surfactant is controversial (17-19).

With shock lung, pulmonary edema can progressively worsen in the presence of left heart failure with subsequent increase in pulmonary capillary pressure resulting in disruption of the vessels into the alveolar space. Pulmonary hemorrhage is the worse event of the asphyxiated lung. Management includes increasing peak end-expiratory pressure in an attempt to tamponade the hemorrhage, limiting deep endotracheal suctioning and correcting homeostasis abnormalities (8).

Renal

Renal involvement occurred in 42% of the infants and presents as oliguria and azotemia (1). The cause of acute renal failure in newborn is attributed to asphyxia in 53.4% of the cases (20). The reason can be either pre-renal due to fluid restriction or inadequate blood volume or renal because of direct effect of asphyxia causing acute tubular necrosis. Elevated urine retinol binding protein and myoglobinuria, decreased urinary output, early rise in creatinine are features of renal failure (21). Studies have shown that asphyxiated newborns who develop renal failure are at greater risk for long-term neurologic sequelae and a worse

overall prognosis (22). Early predictors of renal failure are urinary NAG and beta-2 nicroglobulin and their concentrations were correlated with the severity of perinatal asphyxia (21). Luciano et al (23) indicated that decreased Doppler renal flow systolic velocity observed in asphyxiated neonates on the first day of life is a useful predictive index for subsequent development of acute renal failure with 100% sensitivity and 63.6% specificity. Treatment is supportive. IV fluid and dopaminergic doses of dopamine (2-3 microgram/kg/min). are administered to improve renal blood flow. Dialysis may be required (24).

Gastrointestinal

The significantly asphyxiated neonate is at risk for bowel ischemia and necrotizing enterocolitis (NEC). Clinical signs and symptoms to alert the physician the infant may be developing NEC are feeding intolerance, abdominal distension, abdominal erythema, bloody stools. The onset of NEC usually occurs once enteral nutrition has begun. Therefore enteral feeds are delayed by several days to a week from the initial injury to assure recovery of the intestines. Feedings may be initiated with a volume of 10-20 cc/kg/day and may be increased as tolerated.

Asphyxia may cause significant hepatic damage. Hepatic failure usually manifests itself with hypoglycemia and decreased clotting factors leading to bleeding and increase in liver enzymes especially SGPT (25). Cholestasis is also present in approximately 10% of asphyxiated infants (26). With liver injury albumin production can be impaired resulting in intravascular dehydration and edema. Progressive peripheral edema, decreased renal perfusion with poor urinary output, increased heart rate, hypernatremia, increase in BUN develops. Administration of a colloid like 5% albumin or FFP at 10 cc/kg may improve the intravascular status if vascular integrity is not disrupted from asphyxia. If albumin is <2 grams/dl, 25% albumin with a volume of 4 cc/kg/day can be administered until levels are normalized. But, if there is considerable capillary leak the cycle can only be broken when vascular stability returns.

Hematologic

Asphyxia reduces the platelet production, compromises platelet function (27,28). Therapy is to maintain platelet count>80000 during the initial 24-48 hours after birth. As the patient stabilizes lower platelet counts (20-30 thousand) can be better tolerated.

Asphyxia causes activation and consumption of coagulation factors. In addition to the direct effect of asphyxia on the clotting cascade, liver dysfunction results in decreased production of clotting factors, resulting in worsening coagulopathy (8,29).

In the presence of PT/PTT, thrombocytopenia, and low fibrinogen, administration of corrective blood products is recommended to maintain hemostasis. FFP (10cc/kg) is used to correct PT/PTT abnormalities and cryoprecipitate (1/2-1 phresis) can be used if fibrinogen level is low.

Polycythemia is not an uncommon finding in the asphyxiated neonate. The high hematocrit may be a reflection of the hypoxic environment of the fetus. Treatment of partial exchange transfusion should be initiated in a symptomatic infant to reduce the risk of injury from hyperviscosity syndrome.

In contrast to polycytemia, an affected infant will experience anemia due to bone marrow suppression secondary to asphyxia or an acute blood loss may exacerbate the anemia. Clinically, anemia will present with hypoxemia, tachycardia and acidosis. It is advised to maintain hematocrit above 40% for adequate oxygen delivery. If the delivery is traumatic a bed side sonography will help to rule out intracranial bleeding.

Metabolic

Hypocalcemia and hypoglycemia are common laboratory findings in asphyxia. Both can be easily corrected through intravascular administration of glucose or calcium. Current approach is to maintain glucose between 70-120 mg/dl (8).

Intrinsic thermoregulation of an aspyhxiated newborn can be disrupted, especially when brain stem injury has occurred or with subdural hemorrhage. Temperature instability lead to suspicion that the patient is septic resulting in a workup to rule out infection.

Central Nervous System and Neuroprotective therapy

Treatment of perinatal hypoxic damage remains a cocktail of different mixtures of interventions aimed at reducing selective neuronal necrosis (apoptosis) or infarction of cerebral tissue. Brain-oriented therapy includes pharmacologic and nonpharmocologic interventions. Drugs currently under investigation to prevent severe brain damage include inhibitors of oxygen free radical generation and free radical scavengers, antagonists of excitatory amino acids, calcium channel blockers and nitric oxide synthase inhibitors. There is strong

experimental evidence that local cerebral hypothermia (head or whole body cooling) started before postischemic seizures has a neuroprotective effect, reducing neuronal damage.

Hypothermia

Mild hypothermia is defined as a reduction in core temperature of 1-3°C, moderate as 4-6°C, severe as 8-10°C and profound as 15-20°C (30). Hypothermia is a promising method for neuroprotection because its action is against all the adverse events when applied immediately after the asphyxictic insult. Hypothermia reduces the rate of oxygen-requiring enzymatic reactions and cerebral oxygen consumption, slows the fall of PCr/Pi and confers a protective effect on the brain after ATP exhaustion. Additional experimental evidence suggests that hypothermia suppresses cytotoxic excitatory amino acid accumulation, inhibits nitric oxide synthase activity, decreases interleukin-1? levels, decreases the releases of other cytotoxic cytokins by microglial/glial cells, and suppresses free radical activity, and delayed cell death by apoptosis (30,31).

The efficacy of hypothermia is dependent on a number of factors; timing of initiation of cooling, its duration and the depth of cooling attained. The main controversy between the two modes of hypothermia is whether or not selective hypothermia can effectively cool the deeper brain structures to render the same level of protection that has been demonstrated in animal models of hypothermia. It was suggested that selective head cooling also has the same effect as whole body cooling (32). Recently Shankaran, et al (33) reported that whole-body hypothermia for neonatal encephalopathy with a commercially available cooling system (Blanketrol II Hyperthermia-Hypothermia system). The pilot study in term infants with encephalopathy using this cooling system demonstrate feasibility of initiating whole-body hypothermia at<6 hours of age to a constant esophageal temperature (34.5°C) using servo control. Potential adverse events of hypothermia are increased blood viscosity, mild metabolic acidosis, cardiac arrhythmias, decreased oxygen availability, dysfunction of cellular immunity, coagulation abnormalities and platelet dysfunction, intracellular shift of potassium and choreic syndrome(34).

There is general aggreement that in hypoxic-ischemic injury of the brain, a cascade of biochemical events that evolves over hours to several days happen. Critical issue seems to be the timing in treatment. Charles Palmer (35)in his lecture about neurobiology of perinatal asphyxia described four phases after hypoxic-ischemic insult and treatment strategies were planned according to these phases of recovery (Table II). The interval between the end of hypoxic insult and first 8 hours is defined as latent phase. The first few hours of the latent phase is the reperfusion phase. In the phase of reperfusion-first 4 hours, there is a return of oxygenated blood to previously ischemic brain. Free radicals are generated, activated neutrophils adhere to vascular endothelial cells. In this stage it is important to prevent delayed postischemic hypoperfusion. Reducing the oxygen and glucose requirements of the brain would be helpful. The

Table 2. Current Management and Future Therapies of Hypoxic Ischemic Injury

Reperfusion phase of recovery (0-4 hours)	Latent phase (0-8 hours)	Phase of secondary energy failure (8-48 hours)
Avoid hyperoxemia, hyperviscosity, maintain normal blood pressure, C02, and glucose level	Specific inhibitors of NO	Specific inhibitors of NO for Nitric oxide/peroxynitrite
Free radical scavengers; Allopurinol, ascorbic acid, deferoxamine, Vit E	Calcium channel blockers (nimodipine)	For apoptosis: caspase inhibitors, growth factors
Antineutrophile, anticytokine agents (pentoxifylline)	Excitatory amino acid antagonists, glutamate release inhibitors (lubeluzole, lamotrigine)	Excitatory amino acid antagonists, glutamate release inhibitors (lubeluzole, lamotrigine)
Rescue hypothermia	Prolonged rescue hypothermia	Phenobarbital for seizures (40mg/kg before seizures?)
Ibuprofen for hypoperfusion (no reflow)	Calpain inhibitors for Proteases	

use of free radical scavengers, e.g. allopurinol, vitamin E could be beneficial. Magnesium sulphate has vasodilator, antioxidant, and anticytokine effects, but its potential benefit and safety are controversial (36). In this stage experimental therapies include free radical scavengers, antineutrophil and anticytokin agents (35,37).

In Latent Phase, which is characterized clinically by absence of seizures (pre seizures) and reduction in early cytotoxic edema there is a relative neurophysiological suppression. However biochemical events occurring in the parenchyma and microvessels contribute to injury. Hypoxia-ischemia results in depletion of ATP and the reduction of resting membrane potentials in neurons and glia (primary energy failure). Increased excitatory amino acids, intracellular accumulation of calcium, dysfunction of calcium-binding proteins, activation of nitric oxide synthesis, formation of peroxynitrite, production of free radicals all contribute to neuronal damage. In the phase of secondary energy failure phase (8-48h after reperfusion) coincides with the onset of cytotoxic edema and seizures. Seizures begin at about 7 hrs after reperfusion and peak at about 28hrs. At the same time there is an accumulation of excitotoxins, increased production of nitric oxide, and a fall in brain electrical activity (35).

Apoptosis and delayed cell death

Very severe hypoxic ischemic insults can cause necrosis with destruction of cellular membranes due to total mitochondrial failure. Less severe injury can trigger apoptosis. Caspase family of 'cell death enzymes' is activated in the initiation and execution of apoptosis. Inhibition of apoptosis will take place in the treatment of HIE. The over expression of bcl-2 using herpes simplex viral vectors has shown to limit neuronal death when administered prior or following focal cerebral ischemia (38). Combinations of antiexitotoxic and antiapoptotic therapies are promising for the prevention of further damage.

The recovery interval beyond 3 days can be regarded as the late phase of recovery.

Treatment of complications:

Seizures

It is important to recognize and treat seizures as early as possible. Seizures can increase CNS metabolic demand, cause the release of excitatory amino acids, lead to fluctations in systemic arterial pressure and may cause hypoxia and hypercapnia. Phenobarbital is the drug of choice. It is usually continued until the EEGis normal and there are no clinical seizures for>2 months. The benefit of prophylactic therapy remains controversial. In a randomized control trial prophylactic barbiturate thiopental therapy did not effect the neurologic outcomes and mortality rate of the infants and seizure activity was 75% in both groups. Evans and Levene (40)reviewed 5 studies which met the criteria they proposed and concluded that prophylactic use of anticonvulsant therapy had no benefit on preventing severe neurodevelopmental disability or death. Recently Hall et al. (41)conducted a randomized, controlled, prospective study in term newborn infants with severe perinatal asphyxia. Phenobarbital therapy (40mg/kg before seizure) was associated with 27% reduction of neonatal seizures and newborns who received phenobarbital had a significant improved outcome at three-year follow-up.

Cerebral edema

Brain swelling is not the primary event in HIE and usually occurs after the first or second day of life in association with cerebral necrosis in full-term infants. Lupton et al (42) examined 32 asphyxiated term newborns and only 7 had severely elevated pressures that reached maximum levels at 36-72 hours of age. Levene et al (43) investigated the effects of mannitol in infants with increased ICP, they concluded that ICP decreased and cerebral perfusion improved but other studies do not support their data. The main strategy is to prevent fluid overload. Current data do not support routine use of steroids and mannitol.

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) may complicate the care of patients with severe HIE. This syndrome is due to the decreased excretion of free water and its consequences; therefore it should be treated with careful fluid restriction SIADH is characterized by hyponatremia, low serum osmolality and high urinary osmolality with continued excretion of sodium, in spite of fluid overload with bulging fontanel.

As a conclusion, supportive treatment is the basic approach to prevent from further neuronal damage. For this reason maintaining adequate ventilation, adequate cerebrovascular perfusion and adequate blood glucose levels is essential. However hypoxic-ischemic injury of the brain is a complex event that during the phases of recovery,

cerebral damage still continues. Rescue hypothermia and various pharmacologic agents are in clinical use for neuroprotection and newer ones will be added in the future.

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Evaluation of Oxidative Stress

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SUMMARY

The main structure of human body is cells. To evaluate the function of the cell (especially mitochondria) is nowadays indirectly estimated from the perspective of blood. The values are different in arterial, capillary, venous blood and in intercellular structure. In order to make a correct estimation, all blood values must be altogether discussed under the patronage of clinical evaluation (including neurological, respiratory and other organ system functions, also concerning gut/liver, immune response).

Blood gases are classified as; a)Blood gases; pH, pCO_2, pO_2, b)Oxygenation: ctHb (Total blood hemoglobin concentration = cO_2Hb-oxy + cHHb-deoxy + cCOHb-carboxy + cMetHb-met), Hctc, sO_2 (Make correlation with ctHB, oxygen saturation = $cO_2Hb/cHHb + cO_2Hb$), FO_2Hb (Oxyhemoglobin ratio = $cO_2Hb / cO_2Hb + cHHb + cCOHb + cMetHb$), FHHb, FmetHb, FetalHb, c)Electrolytes: Na, K, Ca, Cl, d)Metabolic values: Glucose, lactate, bilirubin, mOsm, e)Status of oxygen: ctO_2 (Content = Hb (g/dl) x 1.34 ml O_2 / g Hb x saO_2 x (0.003 ml O_2/mmHg/dl), p50, f)Acid-base status: cBase, $cHCO_3$, ABE, SBE, AG (Anion gap = $[Na + K] – [Cl + HCO_3]$).

The values will be taken arterial and venous simultaneously. After the treatment the values can be affected between 2-5 minutes. If you don't obtained any response, then change your approach. Don't just give intravenous fluid, but make reperfusion, prevent the baby from ischemic perfusion complications and edema.

The values are not taken individually. We have to discuss the correlations with the concerning parameters. E.g. baby A with paO_2 85 mmHg, saO_2 95%, Hb 7 g/dl, is more hypoxemic than the other baby B with paO_2 55 mmHg, saO_2 85%, Hb 15 g/dl. CtO_2 is 8.9 in baby A, but in baby B 17.1 mlO_2/dl.

All for one, one for all will be the main topic for evaluation of blood gases. All the components will be systematically examined and must be correlated with the clinical findings.

The main unit for living organisms is cell. The vital importance is primarily the viability of the cell. All organ systems were established for proper cell functions. The functional status of the cell have to be in good coordination and correlations with the organ systems. For oxygenation at least respiratory, circulation, metabolism, hematological and osmolarity of the body must altogether work well. One cell must be in coordination with all the body and with other cells. Therefore the organ systems must be in balance.

We cannot directly look inside of the cell. We can only estimate the functions, by clinically (activity, cerebral functions etc), by equipments like EEG, EKG etc., by the balance of the living status. The main tool for evaluation of the cell is nowadays by the blood gases.

In the presence of alkalosis or acidosis, one must think that the defense mechanisms are in action. Due to the systemic inflammatory/oxidative response, several unexpected events take place. The main goal is to protect the cell. If the condition is inevitable, then the first step is to overcome the first stage of hypoxia (Table 1), before the dysfunction begins.

There is a close correlation between the causative factor (e.g. oxidative stress) and the tissue reactions. This interaction is indicated at the Table 2. There are at least 9 different clinical presentations of problems (9 is the severest, 1 is the slightest). X-ray, ultrasound and several other diagnostic methods are used to get information about tissue changes. Severities of the conditions are numbered 1 to 9 levels. Tissues in organ systems are also vulnerable at different severity.

In oxidative stress syndrome multiple organ involvement is noticed. CNS injury (HIE) is occurred in 72%, renal in 42%, gastrointestinal system in 29%, myocardium in 29% and pulmonary in 26% of the infants (1).

Prevention always comes before treatment. As you can see in the Table 2, blood gases may indicate severe acidosis, but clinical picture may be

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Table 1. The Evaluation of the Cell/Tissue Status

STAGE		STATUS FUNCTION
1.	Biological variation	Variations between the gestational ages and infants.
2	Physiological adaptation	Adaptation mechanisms, stimulus and feedback can control the body.
3	Functional disturbance Metabolic activity increases.	Increase in respiration, deep breathing, heart rate etc. No any injury.
4	Compensation period	Compensatory phase of acidosis and alkalosis. Metabolic problems.
5	Reaction of tissues started	Vasoconstriction, pooling, interstitial edema, central flowing of blood and systemic inflammatory reactions started.
6	Disturbances begin	Cellular functions will be delayed, halted, ineffective and reactive states (e.g. Hypoxic Ischemic Encephalopathy (HIE) begin.
7	Degeneration	Vacuolar, hydropic cells and vasogenic edema develops. Histopathological findings are noticed. Changes in mitocondria
8	Rupture of the membranes	Erythrocytes; burr and acantocytosis or degenerated. Cell organelles are in the circulation, bursting of cells by complement.
9	Tissue reactions edema, Graft Versus Host, fibrosis.	Tissue reactions, degenerations, hemorrhages, scleredema, cytostatic
10	Cell and/or tissue death	Lyses of erythrocytes, necrosis.

Table 2. The Correlation of Tissue Reactions and Severity of the Cause (9 point is the severest, 1 point is the slightest condition)

SEVERITY OF	Severe	5	6	9
THE CAUSATIVE	Medium	2	4	8
FACTOR	Slight	1	3	7
		Slight	Medium	Severe
		DIFFERENT	TISSUE	REACTIONS

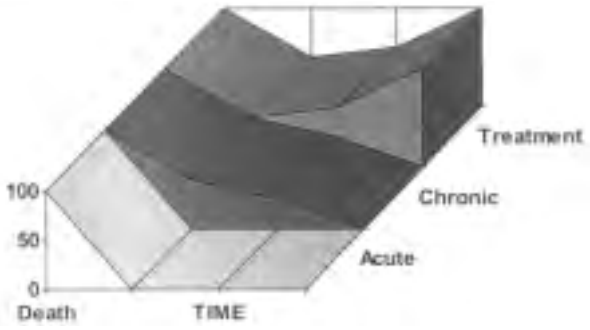

Figure 1. *The duration of tissue reactions in acute, chronic and treatment phases. (100 value means healthy, 0 means death)*

mild. It's vice versa. Therefore clinical evaluation must be carefully performed, not once, but for every 15 minutes. After the perfusion, we can aware of the change within 2 minutes, and in 10 minutes the action can be fully noticed. Try to prevent the baby from oxidative stress, not to treat the hypoxia. First rule is not to be harmful (primum non nocera) for every medical application.

If we consider the time factor, the reactions can be categorized as acute, sub-acute or chronic.

When the problems develop very fast and severe, death is inevitable before the tissue reactions develop. In chronic state or in the case of treatment, the symptoms and clinical findings (tissue reactions = systemic inflammatory and/or oxidative response syndrome) were encountered. The healing have to be needed a time. This duration is symbolized in Figure 1.

The clinical features, like cyanosis, inactivity, edema etc. can be noticed in the condition of the compensation, the critical period. But nowadays the main important issue is the estimate the oxidative stress before symptomatic state. Hypoxia triggers the other mechanisms. In the compensation period, it's hard to estimate the clinical severity. We have to go into cell to evaluate. But at current practice, it's not possible to get recordable values from outside of the cell membrane. They are indirect values.

Parameters of blood gases can be classified in 4 parameters. They are; a) Blood gases; pH, pCO_2, pO_2, b) Oxygenation: ctHb (Total blood hemoglobin concentration), Hctc, sO_2 (oxygen saturation), FO_2Hb (Oxyhemoglobin ratio), FHHb, FmetHb, FetalHb, c) Electrolytes: Na, K, Ca, Cl, d) Metabolic values: Glucose, lactate, bilirubin, mOsm, e) Status of oxygen: ctO_2 (Content), p50, f) Acid-base status: cBase, $cHCO_3$, ABE, SBE, AG (Anion gap).

Blood Gases: 1) Oxygen: Atmospheric oxygen

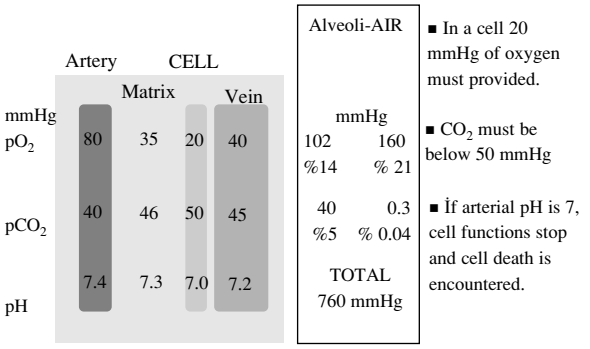

Figure 2. *Oxidative pressures in tissues (3).*

pressure which is 160 mmHg is needed to be reduced at 20 mmHg in the endoplasm (Figure 2). For the passage of oxygen, from alveolar space to blood, 11 mmHg gas pressure difference is required. This pressure difference must be 24 mmHg in edema or premature state. Ventilation to perfusion ratio is not 0.8 for every condition. Hypoventilation, inter-alveolar space widening (prematurity is a factor), especially inter-alveolar shunts, atalectasis, closing capacity, less residual volume problems and surfactant insufficiency create problems in oxygenation. The oxygen exchange can be performed 1/3 of time of ventilation. This means that, giving oxygen to a baby by ventilators, doesn't mean that you can increase the pO_2 levels of the blood. Since PaO_2 reflects only free oxygen molecules dissolved in plasma and not those bound to hemoglobin. PaO_2 cannot tell us 'how much' oxygen is in the blood, for that you need to know how much oxygen is also bound to hemoglobin, information given by the SaO_2 and hemoglobin content (2).

2) Carbon dioxide: Organic substances are composed of carbon. There are chemical bonds between the carbon atoms. These bonds are transferred to ATP at the mitochondria. The inorganic CO_2 is the end result of energy metabolism. This must be carried to the atmosphere from the cell. For diffusion 1 mmHg pressure difference is enough. CO_2 is 20 times more potent than O_2. Therefore the main problem is oxygen transport. If CO_2 is increased in the blood, the tissue is badly damaged. But in Heldan effect CO_2 is also transported by the hemoglobin. The diffusion period is nearly takes 2/3 of ventilation. It's mainly in 1/3, but because of HCO_3 buffering system, it needs time for transportation (4).

3) pH: Function of the buffering system is to maintain normal pH value. For HCO_3 diffusion the pK is 6.1. Therefore for pH 7.4 value (pH = pK + Base/Acid) exactly 24 mmol base / and 1.2 mmol CO_2 is needed.

4) Acid-base status: If the pH is within the normal range, but the $PaCO_2$ and/or HCO_3 (or both) are abnormal, then there is compensation. An acid-base derangement exists. Respiratory compensation is very fast, occurring within seconds or minutes. This compensation occurs via the body's control of respiratory rate, through the brain respiratory center. Thus respiratory compensation for metabolic abnormalities is seen almost immediately. Metabolic compensation, on other hand, is slow. It occurs through elimination of acid or alkali by the kidney. Hours go by, before significant compensation is seen. Metabolic correction through the kidney will be seen for metabolic disturbances (5).

Oxygen transport of Hemoglobin (Oxygenation): Diffusion of gases is not satisfactory for the 20 mmHg oxygen content of the cell. Hemoglobin is required for the transportation. Every hemoglobin molecule has different oxygen transport capacity and biologically different molecular actions. Oxygen must bind not in chemically but in physically for easy transportation. Blood hemoglobin concentration is very important. Total blood hemoglobin concentration (ctHb) indicates oxyhemoglobin (cO_2Hb), deoxyhemoglobin (cHHb), carboxyhemoglobin (cCOHb), methemoglobin (cMetHb) (6). We have also noticed saturation and oxygen contents. E.g. baby A with paO2 85 mmHg, saO_2 95%, Hb 7 g/dl, is more hypoxemic than the other baby B with paO_2 55 mmHg, saO_2 85%, Hb 15 g/dl. Oxygen content (ctO_2) is 8.9 in baby A, but in baby B 17.1 mlO_2/dl. Oxygenation is 2 times better than baby A.

Status of oxygen: Transfer of the oxygen to the cell is important. In this case the oxygen content is important. Fetal hemoglobin oxygen content is more than the adult hemoglobin. But oxygen transferring capacity of adult hemoglobin is higher than the fetal Hb. Adult hemoglobin is generous, but fetal hemoglobin is miser. Fetal hemoglobin can take oxygen at low concentrations which is necessary for fetal life.

Electrolytes and osmolarity: Living organisms are mostly composed of water. Water can allow the molecular activity by biochemical ways, without energy consumption. By means of hydrogen covalent bonds, diffusion is easily performed. There must be osmotic balance. This ionic effect causes the attraction between negative (oxygen) to positive (Na, K, Ca) and positive (Hydrogen) to negative (Cl) (7). This makes a great diffusion activity in the fluid matrix, about 100 million times per se-

cond. If the balance is not established, swelling or shrinking of the cells are noticed (Figure 3). The macromolecules and the membranes of cells attract the molecules and form a hydrostatic zone. Electrolytes are important for this attraction.

Free fluid pressure in the matrix is nearly minus 8 cmH2O. If it increases, to + values, we notice the edema. When the free fluid increases, the diffusion decreases. The lymphatic drainage develops after 34-36 gestational ages. This indicates that, great pressure is required to save the fluid into the vascular bed. Capillary colloidal osmotic pressure is important, at this stage. Hydrostatic osmotic pressure mainly depends on electrolytes. Electrolytes are highly transferable to capillary, to matrix and to cell. 300 mOsmol must be obtained in every circumstance (Figure 4).

When the intercellular matrix is degenerated, first interstitial (increase of fluid), than vasogenic (escape of plasma) and cytostatic (extravasations of blood components) edema develops (Figure 5).

Metabolic values: Blood values are not always good indicators for cellular function. We therefore try to estimate the function inside of the cell. For example the blood glucose is increased in diabetic mellitus but the cell is lack of energy. The glucose

mmol	CELL	MATRIX
Na	14	146
K	140	4.2
Cl	4	105
HCO3	10	27
Glucose	(8.7)	5.6
Protein	40	5
Urea	4	4
TOTAL	302.2	302.9
in mmHg	5430	5453

• All living organisms must perform an osmotic balance.

• Cell and surrounding matrix must be in physio-biochemical balance.

Figure 4. *Inter and extra cellular interactions (3) (osmolarity in mmol, pressure in mmHg)*

combines with phosphorus and forms Glucose 6 Phosphate. After the consumption of glucose for energy requirement, lactate, private, ammonium, ketone bodies are formed, due to the different metabolic pathways, whether oxidative or anaerobic (8). All are good indicators. Comparisons of values are more important.

Perfusion, reperfusion: Adequate circulation of blood is vital importance. Blood is composed of fluid matrix in which molecules are transported. If diffusion is impaired, the circulation is directed at the central sites. Capillary and peripheral circulation is nearly stopped. In vasoconstriction only plasma flows. Erythrocytes are cumulated and forms cloth. Fibrinolysis, consumption coagulopathy, chain reactions begin. There will be no oxidative stress at the beginning, later the most advanced develops. It is nearly the same in vasodilatation, in which impaired circulation develops due to the pooling of blood.

Administration of intravenous fluids has a direct effect on the electrolyte balance. To support the capillary diffusion, osmolarity controlled fluids, like diluted dextran's or plasma, can be added to the i.v. fluids. While considering the diffusion of capillary, we should care of the ischemic perfusion damage to the tissues at this reperfusion stage. One must consider the prevention of reperfusion injury at the beginning of the perfusion.

Dopamine like cardiovascular drugs must be selected. Dosage must be justified due to the condition of the baby.

The other important one is portal system circulation. Attention must be drawn to the portal system. If you reduce the flow, toxins and micro-organisms are passed from intestine to blood. NEC must be prevented.

Bilirubin is one of the first encountered liver functions of the body. Therefore if we considered

the bilirubin for the metabolism of the liver and entero-hepatic circulation system, we will not try to overcome hyperbilirubinemia at the first week of life.

Clinical Findings (Apgar score): APGAR is a clinical scoring system which is a combination of several organ systems. It's a good predictor for clinical status of the baby. We have to protect the baby before the tissue reactions begin. Brain functions give us clues about the cell function. If a baby is depressed, it means that something is going to wrong to the baby (9).

Close Bedside Physician Care (CBPC): If you want to be a good doctor for your baby, please sit near to the incubator and try to understand what is going on. The books, consultants, professors of Neonatology can help the physicians and they will give some information. But the reality is the baby.

CONCLUSION: From outside of the house (cell), it's hard to see the inside. From inside, outside can be seen. Values from the blood are only an indicator of the vessels. For good estimation and evaluation, all for one, one for all will be the main philosophy. All the components will be systematically examined and must be correlated with the clinical findings. Close Bedside Physician Care is the prime important.

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New Placental Vasoactive Factors and Gestational Diseases

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During normal pregnancy, important physiological adaptations occur in the mother which assure an adequate blood supply to the fetus. Vascular resistance, mean arterial pressure, and sensitivity to endogenous constrictors are reduced, in addition to increased cardiac output, heart rate, and blood volume. Alteration of these haemodynamic adaptations to pregnancy is associated with conditions critical to fetal well-being such as pre-eclampsia (PE) and intrauterine-growth retardation (IUGR), characterized by endothelial dysfunction. The human placenta is a multifunctional organ providing oxygen, water homeostasis, nutrition and endocrine messages for the fetus until delivery. Impaired placental perfusion is associated with reduced transfer of oxygen and nutrients from the mother to the fetus. Consequently, fetal growth and oxygenation are reduced resulting in intrauterine growth retardation (IUGR) and fetal hypoxemic hypoxia. In humans, increased placental resistance may be the result of different factors: reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary stem villi, increased vasoconstriction at villous level because of local release of vasoactive substances, e.g. thromboxane or endothelin, or decrease of vasorelaxant agents. These alterations are triggered by ischemia of the intervillous space due to reduced utero-placental perfusion.

The mechanisms involved in the control of fetal-placental vascular tone remain to be clearly characterized as well as the physiological response of the fetus to adverse circumstances during pregnancy. Since placenta lacks autonomic innervation, vascular tone at this level is regulated by the action of endothelial derived factors; thus it is well defined the central role of the vasoactive substances produced by the placenta and by the fetus himself in the regulation of placental and fetal circulation. Among these substances a key role may be played by some newly discovered agents such as adrenomedullin (AM), nitric oxide (NO) and endothelin (ET-1) in physiological and pathophysiological conditions. In this light, we have investigated the potential role of these vasoactive factors in some gestational diseases such as PE, IUGR and gestational diabetes, conditions in which there are evidences of endothelial dysfunction.

We measured AM, NO and ET-1 concentrations in maternal, fetal and placental compartment by means of specific RIA, moreover, we investigated their prevalence and distribution on placental tissues and cord by means of immunohistochemistry.

Endothelin

Endothelin (ET) is a 21-amino-acid peptide made by from pre-pro-ET (200 amino-acids) and pro-ET (38 amino-acids, called "big-ET") by a cleavage performed by an ET converting enzyme (ECE) (1). The family of endothelin peptides (ET) consists of three distinct isoforms: ET-1 (the original porcine and human ET), ET-2 (with two amino-acid substitutions), and ET-3 (with six amino-acids substitutions) coded for by three separate genes in the human, rat, and porcine genome (2). ET was first cloned from a human placental cDNA library, it has been demonstrated that the human placenta, and uterus, have specific high-affinity receptors for ET and that the peptide increases vascular resistance in the fetoplacental vasculature. ET-induced pressor responses are of long duration and are associated with an involvement of other vasoactive substances. The data are compatible with a role of ET as an endogenous modulator of the fetoplacental circulation in humans. ET-1 has been localized in placenta and fetal membranes (3), and mRNA for ET-1 has been found in endothelial cells of placental villi and in avascular amnion of fetal membranes (4). Accordingly to other studies (5-7) we fo-

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und that in PE and IUGR pregnancies ET-1 concentrations in placental compartment were higher than in normotensive pregnancies (8). Among complicated pregnancies, amniotic fluid levels were significantly higher in patients with PE associated to IUGR than in PE alone women. We demonstrated increased concentrations of ET-1 also in pregnancies complicated by gestational diabetes (9). All these conditions are characterized by endothelial damage, and higher levels correlated with a more severe impairment of placental vasculature, with reduction of blood flow to the fetus. ET-1 may play a significant role in determining a potent vasoconstriction of placental vessels, and activating other factors (e.g prostaglandins, thromboxane A2, PAF) responsible for the hemodynamic alterations. ET-1 production by placental tissues may precede and thus contribute to the development of increased placental vascular resistances. Alternatively, the elevated ET-1 levels may be the results of endothelial damage associated with increased placental resistances.

Nitric oxide

Nitric oxide (NO) is a potent vasodilator released from L-arginine by endothelial cells that plays a key role in the control of vascular tone in several districts. There is evidence that NO is released by the feto-placental tissues. NO synthase is present in the human fetal-placental tissues and endothelial NO synthase mRNA has been detected in the placental villi (10). Furthermore several groups have reported that NO donors such as glyceryl trinitrite or L-arginine relax human umbilical artery and NO decreases perfusion pressure of the human fetoplacental circulation (11,12). These studies indicate that NO produced by fetoplacental tissues may contribute to the regulation of blood flow from and to the fetus. In vitro studies have shown the inhibition of NO release in placental circulation induces an increase in arterial pressure, amplifying vascular response to vasoconstrictive autacoids. Several studies have addressed NO production in PE, although resulting are conflicting. Maternal serum, urine and cord blood NO metabolites concentrations are reported increased, reduced, or unchanged in preeclamptic women (13,15). Recently a calcium-dependent nitric oxide synthase (NOS), corresponding to the endothelial isoform of the enzyme (eNOS) has been localized on syncytiotrophoblast and endothelial cells of human placental villi and its activity assayed in placental extracts (16). In a recent study we found that amniotic fluid NO concentration was significantly higher in PE women. Moreover, we found that in placental tissues collected from PE the intensity of the staining and the percentage of endothelial cells stained for the eNOS were higher than in the control group. Our immunohistochemical data confirm the study of Ghabour et al. (18) on placental NOS expression in PE, suggesting that, in the endothelial cells of the villi, eNOS expression is enhanced in PE patients and can help to maintain the placental vasculature maximally dilated. The higher concentrations of amniotic fluid nitrate in PE patients may result from the stimulation of placental NOS activity. The significance of this increased activity could be compensatory for the increased synthesis and release of others vasoactive substances (TxA2, ET-1, etc.) from the injured endothelium acting as vasoconstrictors on placental vasculature. This hypothesis is supported by the finding of increased NO levels in amniotic fluid of IUGR pregnancies with normal feto-placental haemodynamics, whereas NO metabolites concentrations are significantly reduced in IUGR with abnormal uterine artery resistance index. Furthermore, nitrite levels in amniotic fluid correlated inversely with uterine resistance index and the umbilical artery PI/fetal middle cerebral artery PI ratio, an index of fetal redistribution of circulation which is characterised by peripheral vascular contraction and cerebral vasodilatation (19). These data suggest that in IUGR pregnancies a compensatory increase in the synthesis of NO within the placenta may occur in an attempt to maintain an adequate blood flow through the placenta. When NO production decreases, resistance in utero-placental and fetal-placental circulation markedly increases, compromising fetal haemodynamics. This offers the rationale for the use of NO-donors in IUGR pregnancies complicated by IUGR with impaired utero-placental circulation.

Adrenomedullin

Adrenomedullin (AM) is a vasoactive peptide first isolated in pheochromocytoma produced by endothelial and vascular smooth muscle cells. During pregnancy AM concentrations are significantly increased and high levels are present also in fetal plasma and amniotic fluid (20). The placenta is an important site of production for this peptide during pregnancy, and, because of its vasodilator and hypotensive effects it has been suggested that AM could participate in the physiological modifications of maternal haemodynamic in pregnancy (21). Moreover acting in an autocrine, paracrine manner, it may have a role also in the regulation of utero-pla-

centa and fetal circulation. The placental vessels are relaxed by AM in a dose-dependent manner and AM is expressed in the fetoplacental and umbilical vascular endothelium where basal production of AM contributes to low fetoplacental vascular resistances. AM induces relaxation trough an increase in cAMP with the reduction of intracellular Ca2+, but also indirectly stimulating NO release and inhibiting ET-1 secretion by endothelial and vascular smooth muscle cells (22). Infusion of NO-LA, which acts inhibiting NO production causes an attenuation of AM induced vasodilatation. NO is an important mediator of placental vascular tone, thus regulating blood support to the fetus (23).

Maternal circulating AM has been reported either increased, decreased or unchanged (24-26) , whereas in umbilical plasma and amniotic fluid we found that its concentrations were higher than in normotensive pregnancies (27). Conflicting results have been reported also in the expression of AM in feto-placental tissues in PE. Ir-AM in placentas of PE women was found decreased or unchanged, and AM mRNA expression has been shown to be either decreased or unchanged in the placenta and uterine muscle, decreased in fetal membranes and increased in umbilical artery (28). Recently we found that in IUGR fetuses AM concentration was higher than in normal pregnancy and it correlated with cerebral and peripheral blood flow (29). Of particular significance seems to be the role of AM in the fetal response to hypoxia as demonstrated by the relationship between circulating AM and vasodilatation of fetal cerebral vessels. In another condition associated with endothelial damage such as gestational diabetes we found that AM concentrations in amniotic fluid were higher in pregnant women with diabetes, both preexisting or manifested during pregnancy, than in euglycemic controls whereas no differences were found in maternal circulation (30). This finding suggests an enhanced synthesis or secretion of the peptide by the placental structures that may play a regulatory function, preventing excessive vasoconstriction and inhibiting excessive platelet aggregation. This hypothesis is supported by the finding of a negative correlation between amniotic fluid AM levels and arterial blood pressure in diabetic pregnant women.

Summary

In summary we found that all these newly discovered vasoactive factors are produced by the placental tissues in large amount and are secreted in the fetal compartment where they participate in the regulation of feto-placental circulation. In pregnancy complicated by PE, IUGR and gestational diabetes, conditions associated with impairment of utero-placental and fetal hemodynamics, ET-1, NO and AM secretion is significantly affected.

These findings suggest a potential future use of these vasoactive factors in the clinical management of these pregnancy complications.

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Contribution of Multiple Pregnancies to Perinatal Mortality and Morbidity

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ABSTRACT

Multiple pregnancies have increased from 9 per 1000 pregnancies in the 1970s to 14 per 1000 pregnancies. Multiple births account for 10% of perinatal deaths (8% of fetal deaths and 14% of neonatal deaths). Compared to singletons births, the perinatal mortality rate is four times higher in twins, and nine times higher in multiple births of a higher order. The cerebral palsy rate among survivors is five times higher in twins and nineteen times higher is multiple births of a higher order. Monochorionic monozygotic twins are at the highest risk, due firstly to the cell division process leading to chromosomal or other anomalous lethal aberration in one fetus, and secondly to twin-to-twin transfusion syndrome (TTTS) and its adverse consequences on the surviving fetus if there is fetal death of its co-twin. The incidence of TTTS is 15-30% in monochorionic monozygotic twins. Data are emerging on the obstetric risks, survival and neurological outcome associated with interventions for treating TTTS (serial amnioreduction, fetoscopic laser ablation of placental vascular anastomoses, amniotic septostomy, and selective feticide), and several randomised controlled trials are in progress.

Keywords: Multiple births, perinatal mortality, perinatal morbidity, twin-to-twin transfusion

Introduction

There is a worldwide trend for an increase in the rate of twinning and higher order multiple births from the late 1980s [7, 10, 18]. This has been attributed to increasing maternal age and the increasing use of fertility enhancing therapies [9, 19]. The true incidence of multiple pregnancies is higher than was reported, because for every twin pair born, at least 10 singletons are conceived as one of a twin pair (the vanishing twin syndrome) [2]. The monozygotic twinning rate is constant worldwide at 3-5 per 1000 pregnancies until an unexplained increase recently. The dyzygotic twinning rate is highest in Africa and lowest in the Far East, in between in Caucasians and Indians, and increases with maternal age and parity. Multiple pregnancies, especially those from monochorionic monozygotic twins, are associated with an increased risk of perinatal mortality and morbidity. This can result in serious consequences to the long-term outcome among survivors, including an increased risk of cerebral palsy (CP).

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Incidence of multiple pregnancies

An upward trend for multiple pregnancies in Australia has been documented in the last 20 years. The rate of 9 per 1,000 confinements in 1977 has progressively increased to 14 per 1,000 confinements in 1993 [11]. This national perinatal data collection reported 3,520 multiple pregnancies out of 256,956 fetuses remaining in utero at 20 weeks' gestation. It reported 3,420 twin pregnancies, 99 triplet pregnancies and one quintuplet pregnancy. In Australia, as with other developed countries, the dizygotic to monozygotic (Dz:Mz) ratio for twins was over 2.0, but is now under 1.0 [8, 16].

Perinatal mortality

Fetal death (stillbirth) is defined as death prior to complete expulsion or extraction from its mother of a product of conception of 20 or more comple-

Table I. Fetal, neonatal and perinatal deaths in singleton and multiple births. Based on Lancaster et al, 1996 [11].

	Singletons		Twins		Other multiple births	
	Number	Rate[a]	Number	Rate[a]	Number	Rate[a]
Fetal death	3,878	5.1	315	15.7	22	24.2
Neonatal death	2,498	3.3	371	18.8	44	49.5
Perinatal death	6,376	8.3	686	34.1	66	72.5

[a]Rate per 1,000 births.

ted weeks of gestation or of 400 grams or more birthweight; the death is indicated by the fact that after such separation, the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles. Neonatal death is defined as death of a liveborn infant within 28 days of birth. Based on these definitions, our Australian national data for the three years, 1991-1993, showed that there were 4,215 fetal deaths (5.4 per 1,000 births), 2,913 neonatal deaths (3.7 per 1,000 births) and 7,128 perinatal deaths (9.1 per 1,000 births) [11]. Multiple births accounted for 10.5% of all perinatal deaths (8.0% of fetal deaths and 14.2% of neonatal deaths). Compared to singletons births, the perinatal mortality rate was 4.1 times higher in twins, and 8.7 times higher in multiple births of a higher order (Table I).

Cerebral palsy

A population-based study from the United Kingdom showed that multiple birth infants are at a higher risk of CP compared to those who were of singleton birth [13]. The CP rate was 2.3 per 1,000 in 254,360 singleton survivors, 12.6 in 5,207 twins and 44.8 in 142 triplets. The difference is partly due to the lower birthweight distribution and partly due to the increased risk of CP among multiple births born at more than 2,500 grams. Among the extremely low birthweight (<1000 g) subgroup, the CP rates were 8.6%, 15.8%, and 22.2% in singletons, twins, and triplets, respectively. The higher risk of CP in twins is not entirely explained by their increased risk of prematurity [20]. The infant death and CP rates for a cohort of over 104,000 live births reported for different gestations from that study are shown in Table II.

Monozygotic versus dizygotic twins

Mz twins are at considerable higher risks than Dz twins. Firstly, in Mz twins, the cell division process leads to a chromosomal or other anomalous lethal aberration in the fetus. Mz twins are responsible for the increase in the rate of congenital anomalies in twins compared to singletons [3]. Conjoined twins (1 in 50,000) are a form of Mz twinning in which the division of the zygote is incomplete. Acardia (1 in 30,000) is caused by an imbalance of the interfetal circulation in monochorionic Mz pregnancies. Secondly, twin-to-twin transfusion syndrome (TTTS) can occur and, after the fetal death of one twin, adverse consequences can result in the surviving co-twin. About 70-75% of Mz twin pregnancies have monochorionic placentas in which vascular connections are common. These anastomoses can be superficial (artery-to-artery, vein-to-vein) or deep (artery-to-vein). Most shunts are balanced but an imbalance will result in donor to recipient transfusion. The incidence of TTTS is 1 in 4000 of all pregnancies and 1 in 60 of twin pregnancies. It is as high as

Table II. Infant death and cerebral palsy rates in singleton and twin births. Based on Williams et al, 1996 [20].

Gestation (weeks)	Infant death		Cerebral palsy	
	Singleton	Twin	Singleton	Twin
28 or less	41.0%	54.9%	3.2%	6.3%
29-32	8.8%	8.9%	2.8%	5.1%
33-36	2.5%	2.5%	3.0%	9.0%
37 or over	0.5%	2.0%	0.07%	0.4%

1 in 5 in monochorionic monozygotic twinning (range 15-30%). TTTS can present acutely, with profound haemodynamic imbalance and death of one twin, usually the recipient. It also has a chronic presentation: the recipient (usually appropriately grown for gestational age) developing polyuria, polyhydramnios, polycythaemia, hyperviscosity, intravascular thrombosis, right heart failure, tricuspid incompetence, hydrops fetalis, and hyperbilirubinaemia, and the donor (usually small for gestational age) developing oliguria, oligohydramnios, stuck twin syndrome, abnormal umbilical artery Doppler flow, anaemia, and hypoproteinaemia.

Adverse outcome in monozygotic twins

Death of a co-twin in monochorionic Mz pregnancies can be a result of thrombo-embolisation from thromboplastin being released from the dead twin's tissues, crossing the placental anastomoses, and causing disseminated intravascular coagulation in the surviving twin. However, a more probable explanation is profound circulatory collapse when the vascular resistance falls in the dead fetus, with the surviving twin exsanguinating into the dead twin, and suffering hypoxia-ischaemia from severe hypotension. In the surviving co-twin, there is an increased risk of significant neonatal morbidity [4, 15]. Central nervous system complications had been reported in 72% of cases, including microcephaly, porencephaly and hydrancephaly. This can result in CP, low IQ and severe learning disability. Gastrointestinal complication had been reported in 19% of cases, primarily intestinal atresia. Renal complications had been reported in 15% of cases, for example, renal tubular dysgenesis. Cardiorespiratory malformations had been reported in 8% of cases. Other miscellaneous complications include aplasia cutis. In a national survey from the United Kingdom, Mz twins compared to Dz twins were found to have a relative risk of 18.91 for both twins being stillborn (1.1% vs 0.1%), and 1.63 for one twin being a stillbirth (3.1% vs 1.9%) [17]. Where there is one stillbirth and one livebirth, the relative risk is 2.26 for the liveborn Mz co-twin dying as a neonate compared to a Dz co-twin (7.6% vs 3.2%). Abnormal neonatal cerebral ultrasound findings are common in Mz twins [1, 4, 5, 6]. These were reported in up to 30% in Mz twins compared to 3% in Dz twins, especially after in utero death of the co-twin. Evidence of brain injury was found in 27-35% of twins with TTTS (incidence of periventricular leukomalacia was 10%). Both the donor twin and recipient twin are at risk of brain injury. The rate of CP and developmental delay is high among TTTS survivors (up to 22% reported in one series). In a population study, the rate of CP after the death of a co-twin was reported to be 83 per 1000 (95% CI 57-117), a 40-fold increase over the general population [12]. In addition, the incidence of other forms of cerebral impairment was 115 per 1000 (95% CI 83-153). Together, they result in an overall risk of brain injury of 20% when one twin died in utero and the co-twin survives infancy. In truly monochorionic MZ twin pregnancies, the risk is even higher at 40%.

Outcome of obstetric interventions

Interventions for the treatment of TTTS include serial amnioreduction, fetoscopic laser ablation of placental vascular anastomoses, amniotic septostomy, and selective feticide [14]. Serial amnioreduction improves uteroplacental blood flow and reduces rate of amniotic fluid accumulation. The procedure-related complication rate is 10%. With this intervention, the survival rate was reported as 37-63% and the neurological damage rate 17-33%. Laser coagulation might not be successful, as the anastomoses causing unbalanced TTTS are more likely to be deep rather than superficial. It is an invasive procedure associated with a high maternal morbidity. Further amnioreduction is required in about 20% of cases. With this intervention, the survival rate was reported as 53-80% and the neurological damage rate 4%. Amniotic septostomy creates a puncture in the inter twin membrane to equalises the pressure in the two sacs, thus relieving the pressure on the placenta. The major risk is cord entanglement. With this intervention, the survival rate was reported as 57-83% but the neurological damage rate remains unknown. The selective feticide technique used must not affect the circulation of the surviving twin (fetoscopic cord ligation, ultrasound guided vascular embolisation). It is usually only performed where the death of the co-twin is certain. With this intervention, the rates of survival and neurological damage are unknown. The Cochrane Review did not find any published randomised controlled trial (RCT) in the treatment of TTTS [14]. Three ongoing RCTs have been identified: Y Ville (Eurofetus Group), N Fisk (London, United Kingdom) and K Moise (Chapel Hill, North Carolina, USA).

The Australian and New Zealand TTTS registry

Over a three-year period (1995-1998) 112 cases of TTTS were registered in Australia and New Ze-

aland [6]. The median age at diagnosis was 21.5 weeks (range 14-35 weeks). The oligohydramnios-polyhydramnios sequence was the most common presentation in 84% of cases. Hydrops fetalis developed in 16% of cases. Absent end-diastolic umbilical artery flow was found in 16% (72% of donor twins and 28% of recipient twin). Therapeutic amnioreduction was performed in 92 cases (82%) started at a median gestation of 22.5 weeks. A total of 281 amnioreductions were performed (median 2 per case, range 1-23). The median volume of amniotic fluid removed per procedure was 1725 ml (range 300-5200 ml). Complications reported within 24 hours of the procedure included chorioamnionitis and preterm labour (2 cases), prelabour membrane rupture (5 cases), and umbilical cord entanglement (2 cases). Delivery occurred at a median gestation of 29 weeks (range 18-38 weeks). The prematurity rate was 90% (44% of infants were born <28 weeks). The caesarean section rate was 52%. The fetal death rate was 18%, and the neonatal death rate was 19%. Perinatal survival rate was 63% (recipient 67%, donor 58%). Both twins survived in 46% of the pregnancies, one twin survived in 26%, and both twins died in 28%. In the neonatal period, 27% had an abnormal cerebral ultrasound scan: intraventricular haemorrhage 12%, periventricular leukomalacia 10%, ventriculomegaly without intraventricular haemorrhage 6%, and porencephalic cysts 1%. Renal failure developed in 8%, necrotising enterocolitis in 3%, hypertrophic cardiomyopathy in 3% and severe ischaemia of lower limb in 2%. Prognostic factors that were found to be predictive included gestation at delivery (survival rate was 0% <25 weeks, 26% <28 weeks, and 99% >32 wks), absent or reversed diastolic flow on umbilical artery Doppler velocimetry (associated with a fetal death rate of 56%, and an abnormal cerebral ultrasound in 53%), and hydrops fetalis (associated with a perinatal death rate of 61%, and cerebral and cardiac morbidity in 75%).

Conclusions

Multiple pregnancies are associated with significant perinatal mortality and morbidity and an increased risk of CP among survivors. Their perinatal management consumes a large amount of physical, emotional and financial resources. Adverse outcomes following assisted reproductive technologies are partly due to the increased risk of multiple pregnancies and partly due to preterm and low birthweight birth. This fact and the lack of evidence that the transfer of more than two embryos improves pregnancy rates, make it advisable to limit the number of embryos transferred to no more than one or two per cycle. Perinatal mortality and morbidity are particularly high in monochorionic Mz twins, due to an increased risk of congenital anomalies and the development of TTTS, especially when in-utero death of a co-twin occurs. Results of RCTs of current management strategies for TTTS in these pregnancies are awaited with interest. Long-term neurodevelopmental follow-up of monochorionic Mz children who survive TTTS is also needed.

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The Outcome of Multifetal Pregnancy Reduction in a Perinatal Unit For The Period 1994-2002

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ABSTRACT

THE OUTCOME OF MULTIFETAL PREGNANCY REDUCTION IN A PERINATAL UNIT FOR THE PERIOD 1994-2002

Aims: This study was undertaken to evaluate the pregnancy outcome in women who underwent multifetal pregnancy reduction at a single institution.

Methods: The data reported here reflect the multifetal pregnancy reduction experience of Hacettepe University Hospital Department of Obstetrics and Gynecology, Division of Perinatology from 1994 through 2002.
Pregnancy records were retrospectively reviewed.
In the absence of any abnormal findings, the fetuses most readily accessible were chosen for reduction, usually those most fundal in location. All multifetal pregnancy reduction procedures were performed between 9 and 14 weeks gestation via intrathoracic injection of potassium chloride under ultrasonographic guidance.
The fetus chosen for reduction was the one with suspicious ultrasonographic findings such as increased nuchal translucency thickness or delayed growth in comparison with others.

Results: 100 procedures were performed on 93 pregnancies. Of these pregnancies 64 (71,91%) were triplets, 18 (20,22%) were quadriplets, 6 (6,74%) were quintuplets and 1 (1,12%) was a sextuplet.
Mean age of patients was 30,86±4,24, mean gestational age at MFPR was 10,8±1,03, mean starting number was 3,4±0,8 (3-6) and finishing number was 2.
Fetal loss rates according to starting number of fetues were 6,25% for triplets, 16,66 % for quadriplets, and 28,57% for quintuplets and sextuplets.Total fetal loss rate was 10,11%.

Keywords: Multifetal pregnancy reduction, embryo reduction, fetal loss, immature labour

During the last 20 years, there has been a dramatic increase in multiple births. In a population-based study in Denmark, from 1980 to 1994, it was observed that the twinning rate increased 2,7–fold and the triplet-rate increased 9,1-fold. More interestingly, the proportion of multiple births among infant deaths increased from 11,5 to 26,9% during this period [18]. In a US study from 1980 to 1997, twin births have doubled and triplet and higher order pregnancies have quadrupled [16]

This increase in multiple gestations is partly due to assisted reproductive technologies and ovulation induction agents and partly due to increased age of reproduction in women.

Multiple gestations are associated with an increased frequency of maternal complications and higher perinatal morbidity and mortality [12,15]. The major maternal complications are preeclampsia, postpartum hemorrhage, hydramnios and increased cesarian sections. The neonatal complications are due to prematurity or fetal growth restriction. In a review of 12 publications, it was analyzed that of 707 triplet pregnancies 90% of which were delivered before 28 weeks, the perinatal mortality rate was 119 per thousand.These children had increased incidences of developmental disability and cerebral palsy [3]. There is an obvious socioeconomic strain on the family with high order gestations.

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Complications increase as the number of fetuses increase. In the FIVNAT study stillbirth rate (30,2 versus 13,5) and early neonatal mortality rate (26,7 versus 18,9) were significantly higher in triplets compared to twins [11].

It is well accepted that multifetal pregnancies are best avoided by the use of strict criteria for ovulation induction and and embryo transfer in in vitro fertilization (IVF). However, when such pregnancies occur despite adequate precautions, multifetal pregnancy reduction may improve the outcome of these pregnancies.

Multifetal pregnancy reduction was initially used as a procedure to selectively terminate a fetus affected by a genetic disorder [1]. Later its usage was extended to eliminate one or more fetuses of a multiple gestation pregnancy [4].

There are certain complications associated with MFPR and the ethical issues are still unclear.This study was designed to evaluate the pregnancy outcome in women who underwent multifetal pregnancy reduction from 1995 through 2002 at our center.

MATERIAL AND METHODS

This study is a retrospective review of the outcomes of 93 pregnancies who underwent 100 multifetal pregnancy reduction procedures at Hacettepe University, Department of Obstetrics and Gynecology, Unit of Perinatology from January 1994 to, January 2002. Selective terminations were excluded from the study.

Multifetal pregnancies were referred to the Unit of Perinatology at Hacettepe University, Department of Obstetrics and Gynecology. All of them gave informed consent about the procedure. Pregnancy records were retrospectively reviewed.

In the absence of any abnormal findings, the fetuses most readily accessible were chosen for reduction, usually those most fundal in location. All multifetal pregnancy reduction procedures were performed between 9 and 14 weeks gestation via intrathoracic injection of potassium chloride under ultrasonographic guidance transabdominally.

The fetus chosen for reduction was the one with suspicious ultrasonographic findings such as increased nuchal translucency thickness or delayed growth in comparison with others.

After the procedures, all of the pregnancies were called for a follow-up visit at 1 week and later at monthly intervals.

RESULTS

100 procedures were performed on 93 pregnancies. Of these pregnancies 64 (71,91%) were triplets, 18 (20,22%) were quadriplets, 6 (6,74%) were quintuplets and 1 (1,12%) was a sextuplet.

Mean age of patients was 30,86±4,24, mean gestational age at MFPR was 10,8±1,03 , mean starting number was 3,4±0,8 (3-6) and finishing number was 2.

Fetal loss rates according to starting number of fetuses are summarised in Table I. It can be clearly seen that the fetal loss rate increases as the starting number of fetuses increases.

Around 20% of the deliveries occurred prior to 34 weeks after MFPR, almost half of which were fetal losses (Table 2).

Pregnancy complications observed in the study group are summarised in Table 3.

Table 1. Fetal Loss Rates According to Starting Number of Fetuses

	Loss<20 weeks	Loss btw 20-28 weeks	Total loss
3→2 (64)	1 (1,56%)	3 (4,68%)	3 (6,25%)
4→2 (18)	2 (11,11%)	1 (5,55%)	3 (16,66%)
5→2 ve 6→2 (7)	2 (28,57%)	-	2 (28,57%)
Total loss	5 (5,61%)	4 (4,49%)	9 (10,11%)

Table 2. Gestational Age at Delivery After MFPR

	number	%
Abortion	5	5,61
Delivery btw 20-24 weeks	4	4,49
Delivery between 28-34weeks	10	11,23
Delivery> 34 weeks	70	78,65

DISCUSSION

Table 3. Pregnancy Complications After MFPR

	number	%
Preterm Birth	53	59,55
Preterm rupture of membranes	10	11,23
PIH	8	8,98
Preeclampsia	4	4,49
IUGR	10	11,23
Stillbirth	0	-
Early neonatal death	4	4,49

The total fetal loss rate calculated in this study is similar with certain other multicenter series reported. Fetal loss rate of 337 reduced pregnancies from 1985 to 1992 was 11,86% [5] and of 1453 pregnancies from 1993 to 1996 was 12,3% [10]. Bollen at al compared fetal loss rates after 3 different methods of embryo reduction by several authors and calculated 19,6% loss rate after transcervical aspiration, 12,6% after transabdominal and 9,8% after vaginal approach [6]). The results of a multicenter study from 5 countries revealed that out of 3513 MFPR procedures, the fetal loss rates prior to 24 weeks were 4,5% in triplets, 7,3% in quadruplets, 11,5% in quintplets and 15,4% in sextuplet and higher order pregnancies. [9] In our study since the number of quintplets and sextuplets are too small, the fetal loss rate was found to be 28,5% in this group, which must be further investigated with higher number of cases.

In our series, preterm birth was obseved in 59,55% of the cases and PROM was observed in 11,23%. In a review of the world results of MFPR from 1993 to 1996, preterm birth rate was 47,7% [10]. Prematurity in multiple pregnancies is a problem in terms of both morbidity and long term sequela and for the high costs associated with long needs of neonatal intensive care.

Callahan et al reported that 78% of the high-order (≥3) multiple pregnancy fetuses were admitted to the neonatal intensive care unit (NICU) and the predicted total charges to the family for triplets was 36.558 US Dollars per baby compared to 18.974 US Dollars per baby for twins [7] .Yaron et al found that the reduction of triplets to twins significantly reduces the risk for prematurity and low birth weight and may also be associated with a reduction in overall pregnancy loss [17]. In this study it was revealed that non-reduced triplets have 25% fetal loss rate, compared to triplets reduced to twins with a 6,2 % loss rate and unreduced twins with 5,8- 6,3% loss rate. Haning et al analyzed 274 IVF pregnancies and calculated that at the 8-week ultrasound, each viable fetus could be expected to reduce the duration of gestation by approximately 3,6 weeks and each fetus reduced medically or spontaneously could be expected to prolong the gestation by 3 weeks [13]. Unfortunately only 13-14 % of triplets undergo spontaneos reduction [13,14]. In contrast to the above studies Leondires et al reported that the perinatal mortality, gestational age at delivery and take-home infant rate per delivery were not changed significantly after reduction of 46 triplets to twins when compared to 81 triplets managed expectantly. (13% of which were reduced spontaneously) [14]. Alexander et al compared the obstetric outcomes of 32 twin pregnancies obtained as a result of pregnancy reduction with 42 in which reduction had not been used and found that impaired fetal growth and prematurity were not reversed completely by this procedure [2]. Since there are some studies reporting worse and some other studies reporting better outcome with reduced triplets, the ongoing debate about whether triplet pregnancies should be reduced or not, should be answered by every institution's own neonatology unit statistics.

It seems that there is still a high overall fetal loss rate and prematurity after embryo reduction procedures.The most reasonable approach seems to be a consensus to avoid multiple pregnancies in ART programmes. However there are certain obstacles for such a solution.

The teams in IVF are not always the same as the obstetrical ones who follow up the pregnancies and their obstetrical complications.As a result certain facts are not very well known to these teams. An example is the fact that a twin pregnancy, even though less complicated than triplets induces 42 % of prematurity (of which 55% are less than 32 weeks) and 3% of perinatal mortality [8] . Another fact is that the couples themselves are unaware of the difficulties of multiple pregnancies so that there is a pressure on IVF teams to replace maximum number of embryos. One of the most important shortcoming is that not all teams have a good cryopreservation programme so that they try to replace as many embryos as possible to give their patients maximum chances to get pregnant. However it must always be kept in mind that the real success of an IVF team is not the pregnancy rate but the take- home baby rate and even further the rate of healthy babies with a good developmental outcome in future.For this reason, the prevention of multiple gestations must be the goal of future studies rather than reducing the number once pregnancy is achieved. Every effort must be put in to issue guidelines for the prevention of higher order gestations by multidisciplinary commisions formed by Neonatologists, Perinatologists, Reproductive Endocrinologists and Psychologists.

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Doppler Examinations in AGA and IUGR Fetuses Before and After Maternal Physical Exercise

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ABSTRACT

DOPPLER EXAMINATIONS OF FETAL AND UTEROPLACENTAL BLOOD FLOW IN AGA AND IUGR FETUSES BEFORE AND AFTER MATERNAL PHYSICAL EXERCISE WITH THE BICYCLE ERGOMETER

Objective: To study changes in uteroplacental and fetal circulation after maternal exercise in appropriate-for-gestational-age fetuses (AGA) and intrauterine-growth-retarded fetuses (IUGR).

Materials and Method: 33 women with an uncomplicated course of pregnancy and 10 women with IUGR were examined. Physical stress was caused through a bicycle ergometer with 1,25 W/kg maternal weight. Doppler flow measurements were performed in the umbilical artery, fetal aorta, arteria cerebri media and in the uterine artery. Fetal heart rate was documented by monitoring. Maternal lactate and glucose levels as well as maternal heart pressure were recorded.

Results: No significant changes after cycling could be observed in umbilical and uterine vessels neither in the normal pregnancies nor in pregnancies with IUGR. In contrast, in the fetal aorta an increase of the S/D-ratio was recorded in both groups (an increase of 16% [p<0.01] and 18%[p<0.05], respectively for AGA and IUGR cases). In cerebral arteries a decrease of the S/D-ratio was observed after cycling in both groups (a decrease of 24% [p<0.01] and 13%[p<0.05], respectively for AGA and IUGR cases). In AGA fetuses the S/D ratio of the aorta and a.cerebri media returned to pre-test level by the 18th minute of examination. In IUGR fetuses the S/D ratio of the aorta and a.cerebri media did not return to pre-test levels at the end of the test. Fetal heart rate remained unchanged in both groups.

Maternal blood pressure and heart rate increased during the exertion phase but returned to the initial values at the end of the test. A 21% and 24% (respectively for AGA and IUGR groups) reduction of maternal glucose values after exercise was observed (p<0.001). Lactate values doubled in both groups after exercise (p<0.001).

Conclusion: From the results obtained we conclude that maternal exercise does not significantly alter uterine and umbilical perfusion in AGA and IUGR pregnancies suggesting absence of change in the uterine vascular bed resistance. However, submaximal maternal exercise was followed by a fetal cerebral vasodilatation and an increase of resistance in the fetal aorta which was more evident in IUGR fetuses. This might be due to a circulatory deterioration in those cases.

Keywords: Bicycle ergometer, Doppler ultrasound, exercise, IUGR, pregnancy

As physical stress is relatively easy to standardize, several groups have studied changes in pregnant women as a result of sporting exertion, particularly the measurable physiological changes in the organisms of the mother and child. Although using different types of exercise - produced by ergometer, treadmill and running tests - all authors came to the conclusion that light and medium physical exercise has no significant adverse effect on the mother or the fetus [13, 15, 19].

Doppler flow measurements of the fetoplacental unit after physical exercise of the mother have been performed with varying results by several investigators [1-5, 8-10, 12, 14-16, 18, 20, 21]. Only one study compared Doppler flow in uncomplicated and complicated pregnancies after physical exercise of the mother [7].

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The effect of physical exertion on the fetoplacental unit in pregnancies complicated by intrauterine growth retardation or hypertensive disorders is of special clinical interest, because these fetuses are known to be at risk for long-term neurologic morbidity.

Therefore we conducted a study to investigate changes of the feto-uteroplacental unit after defined maternal exercise including measurements in the third trimester of pregnancy in appropriate-for-gestational-age fetuses (AGA) and intrauterine growth retarded fetuses (IUGR).

MATERIALS AND METHODS

Gestational age was calculated by last menstrual data and a sonographic measurement of the crown-rump length within the first 12 weeks' gestation. IUGR was defined as a fetal abdominal circumference <5th percentile for gestational age of our reference ranges [17].

A total of 33 pregnant women with AGA fetuses and ten patients with IUGR fetuses in the third trimester were examined. Multiple pregnancies, cases with maternal renal disease, maternal diabetes, maternal cardiovascular pathology other than hypertension and fetuses with chromosomal or structural anomalies were excluded from evaluation.

Informed consent was obtained from the patients after detailed explanations of the risks (possibility of uterine contractions, reduced placental perfusion with subsequent hypoxia, circulatory strain for mother and fetus, etc.).

The exercise period began with an acclimatization period of three minutes (30 W), followed by ten minutes of moderate exertion (1.25 W/kg body weight for each women). A bicycle ergometer from Mijnhardt (Mijnhardt-Jäger b.v., Bunnik, The Netherlands) was used.

Immediately after the exercise period Doppler flow measurements were performed by two experienced investigators at the department for prenatal diagnosis and ultrasound at the University Hospital, Department of Obstetrics and Gynecology, Homburg/Saar, University of the Saarland. The test period was 35 minutes. In the IUGR group fetal heart rate monitoring (FHR) was performed for additional 15 minutes before and after the exercise.

The Doppler examinations were performed with an Acuson 128 XP/10 (Mountain View, California, USA) and an ADR 5000 (Kranzbühler, Solingen, Germany) ultrasound equipment with a 3.5 MHz convex scanner. Doppler flow recordings of the umbilical arteries, fetal aorta, arteria cerebri media and the uterine arteries were performed. During all Doppler examinations the patients were positioned semi-recumbent to avoid "vena cava syndrome".

Doppler flow velocity waveforms were obtained from a free-floating central part of the umbilical artery in the absence of body movements, fetal breathing or cardiac arrhythmia with the sample volume covering the whole vessel. Care was taken to keep the insonation angle in the umbilical artery at the lowest possible angle. The fetal aorta was localized in its abdominal part at the origin of the renal arteries. The angle between ultrasound beam and fetal aorta was kept below 55°. The middle cerebral artery was visualized at about 1cm of its origin in the circle of Willis in an axial view. The insonation angle in the middle cerebral artery was always below 15°. Care was taken to minimize fetal head compression, because this is known to influence the flow velocity waveforms of the middle cerebral arteries.

For uterine artery Doppler the transducer was placed in the right or left lower part of the abdomen. Color Doppler imaging was used to localize the main uterine artery cranial to the crossing of the external iliac artery. The examination was repeated on the opposite side. The insonation angle was kept below 55° at the uterine arteries.

For every vessel examined five consecutive waveforms of similar quality were accepted for analysis. The ratio of peak systolic (S) over diastolic (D) velocity (S/D ratio) was determined. Abnormal umbilical, uterine and fetal aorta Doppler results were those >2 SD above the mean for gestational age of our local reference ranges [6]. Fetal brain sparing was supposed when the S/D ratio was <2 SD below the mean of our local reference ranges for the middle cerebral artery [6].

Glucose and lactate levels were measured in capillary blood samples taken from the finger pad before and after exercise ("Monotest-Lactat in Halbmicro-Technik", Boehringer Mannheim). The pulse and blood pressure of the mother was automatically registered at three-minute intervals during the test (Dinamap, Critikon).

The Wilcoxon pair difference test for associated random samples was used for statistical evaluation.

RESULTS

NORMAL PREGNANCIES:

The mean performance on the bicycle ergometer was 79 W (±11 W). Gestational age at delivery was 40.0 weeks (±8 days). The mean birth weight

Table 1: Changes of S/D ratio during exercise in AGA pregnancies (n = 33)

		S/D ratio (Mean ± SD)		
	Before exertion (baseline)	After exertion		
		1.-6. min	7.-12. min	13.-18. min
A.umbilicalis	2.6 ±0.5	2.5 ±0.5	2.6 ±0.5	2.6 ±0.4
p value		ns	ns	ns
Fetal Aorta	4.9 ±1.3	5.7 ±2	5.2 ±1.4	5.7 ±1.8
p value		p<0.01	ns	p<0.05
A.cerebri media	5.6 ±3.3.	4.3 ±1.8	6.1 ±3.9	5.9 ±2.9
p value		p<0.01	ns	ns
A.uterinae	1.8 ±0.6	1.7 ±0.4	1.8 ±0.5	1.8 ±0.4
p value		ns	ns	ns

S/D ratio: Systolic/diastolic ratio
ns: difference not significant
SD: Standart deviation

was 3270 g (±383 g).

Mode of delivery: Twenty four (73%) women delivered vaginal spontaneously, 1 (3%) vaginal operative and 8 (24%) by cesarean section.

Doppler flow results of normal pregnancies (Table 1)

Umbilical artery: The observed S/D ratios were within the normal range before and after exertion. However, in 4 (12%) fetuses the measurements reached the threshold range after exercise.

Fetal aorta: The mean S/D ratio before exercise was 4.9 (±1.3). In 8 (24%) fetuses the S/D ratio was at the threshold range (S/D ratio 6-7) and in 1 (3%) fetus at the pathological range (S/D ratio>7). A significant increase in the S/D ratio was determined following exertion (p<0.01). However, the mean value did not reach the pathological level. An increase in the S/D ratio of the aorta shortly after exertion was observed in 21 (63%) fetuses [(In 5 (24%/ within the threshold range, in 16 (76%) in the pathological range].

A.cerebri media: Before exercise, the S/D ratio was in the normal range in all cases. A significant reduction in the S/D ratio was determined shortly after the exertion phase (p<0.01). Twenty minutes after exertion, the results were almost the same as the baseline records.

Uterine artery: The observed S/D ratios were within the normal range before and after exertion.

FHR: The fetal heart rate remained nearly unchanged before and after exertion (Figure 1). In one case fetal bradycardia (lasting approximately two minutes at the end of the exertion phase) was ob-

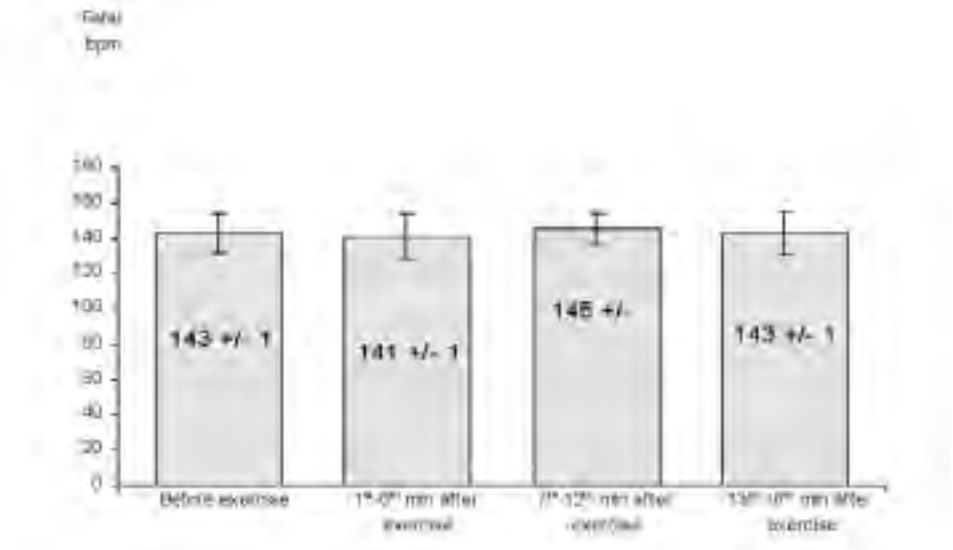

Figure 1. *Fetal heart rate during the test period (mean ± SD) in AGA pregnancies (n=33).*

served. This patient developed preeclampsia in the last two weeks of pregnancy.

Maternal parameters: The maternal blood pressure and the maternal heart rate increased during the exertion phase but returned to the initial values at the end of the test.

The maternal glucose levels decreased by 21% ($p<0.001$) after exercise, while the lactate values increased almost two-fold from 14.6 mg% to 27.6 mg% ($p<0.001$).

IUGR PREGNANCIES:

The mean performance on the bicycle ergometer was 68 W (±10 W). Gestational age at delivery was 37.6 weeks (±19 days). The mean birth weight was 2065 g (±526 g).

Mode of delivery: Five (50%) women delivered vaginal spontaneously and 5 (50%) by cesarean section.

Doppler flow results of IUGR pregnancies (Table 2)

Umbilical artery: In 3 (30%) fetuses the baseline value were in the threshold and in another 3 (30%) fetuses it was pathological. The remaining 4 (40%) fetuses had normal Doppler values. After exercise the S/D ratio was in the threshold range in one (10%) fetus and pathological in 4 (40%) fetuses.

The S/D ratio in the umbilical artery was pathologic in 3 fetuses already before exercise. This had a marked influence on the mean S/D ratio value, because of the very small sample size. Thus, the calculated mean values of all measurements were in the pathological range from the beginning. After exclusion of these 3 cases, S/D ratios became normal and no significant changes in S/D ratios of umbilical arteries occured during the test.

Fetal aorta: S/D ratios before exercise were within the pathological range in 3 (30%) fetuses and in 2 (20%) fetuses within the threshold range. The S/D ratio following exertion rose significantly ($p<0.05$).

Doppler flow measurements after exertion between minutes 1-6, minutes 7-12 and minutes 13-18 showed pathological values in 4 (40%), 5 (50%) and 6 (60%) fetuses, respectively.

The mean values of fetal aortic S/D ratios in IUGR fetuses were higher than in AGA fetuses ($p<0.05$). In contrast to the AGA group, in the IUGR group all S/D ratios after exercise were within the threshold or the pathologic range and did not return to normal values after exercise.

A.cerebri media: The S/D ratio revealed a stepwise reduction until 7 to 12 minutes after exertion ($p<0.05$) and made a "plateau" until 13 to 18 minutes after exertion. In 6 (60%) fetuses the S/D ratio following exertion was lower than the baseline values.

In growth retarded fetuses, the S/D ratios returned to normal levels more slowly than in AGA fetuses. In contrast to AGA fetuses, in IUGR fetuses the S/D ratios at the end remained well below the values registered at baseline ($p<0.05$).

Uterine artery: There were no significant changes in S/D ratios of the uterine vessels during the test.

FHR: The FHRs before and after exercise remained unchanged (Figure 2).

Maternal parameters: Maternal blood pressure

Table 2: Changes of S/D ratio during exercise in IUGR pregnancies (n = 10)

	S/D ratio (Mean ± SD)			
	Before exertion (baseline)	After exertion		
		1.-6. min	7.-12. min	13.-18. min
A.umbilicalis (all)	5.6 ±5.6	5.8 ±5.7	6.2 ±5.3	4.4 ±2.2
p value		ns	ns	ns
A.umbilicalis (without extremes)	2.8 ±0.5	2.9 ±0.8	2.8 ±0.4	3.2 ±0.8
p value		ns	ns	ns
Fetal Aorta 6.5 ±2.8	7.7 ±3.7	8.9 ±5.1	9.3 ±5.3	
p value		p<0.05	p<0.05	p<0.05
A.cerebri media	4.9 ±2.3.	4.3 ±1.6	3.9 ±0.6	4.1 ±1.8
p value		p<0.05	p<0.05	p<0.05
A.uterinae 1.7 ±0.8	2.1 ±0.8	1.9 ±0.5	1.9 ±0.3	
p value		ns	ns	ns

S/D ratio: Systolic/diastolic ratio
ns: difference not significant
SD: Standart deviation

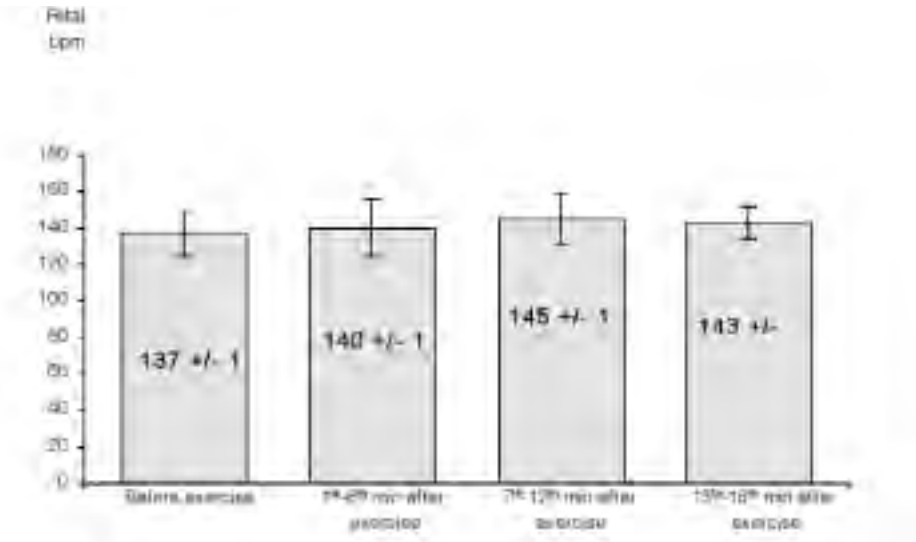

Figure 2. *: Fetal heart rate during the test period (mean ± SD) in IUGR pregnancies (n=10).*

and heart rate increased during exercise but regained normal values rapidly after exercise. The maternal glucose levels decreased about 24% ($p<0.001$), while the lactate concentrations doubled from 11.6 mg% to 24.2 mg% ($p<0.001$).

DISCUSSION

The objective of the study presented was to investigate the relationship between maternal exercise in the third trimester and Doppler flow results of the fetoplacental unit in uncomplicated pregnancies and those complicated by intrauterine growth retardation.

This study reports Doppler flow measurements of the placental vascular bed, the fetal aorta, umbilical artery together with the fetal cerebral arteries in the human AGA and IUGR fetuses after physical exercise of the mother.

There is concflicting data regarding the question of uteroplacental supply during and after physical exercise of the mother in uneventful pregnancies and pregnancies at risk.

In 1956 Morris et al. [11] already studied changes in uterine circulation following physical exertion by the mothers. The authors found a statistically significant lengthening of the uterine clearance half-time of NaCl and hence a reduction in circulation during exertion [11]. At rest, by contrast, the clearance half-time was shorter and uterine circulation improved. The main critic point to the results of this study was that during examination procedure the patient rested in supine position, thus inducing possible vena cava occlusion syndrome.

Several investigators reported of unchanged uteroplacental blood flow and umbilical perfusion after bicycle stress test in the third trimester [3, 10, 16, 18, 20]. Morrow et al. found higher S/D ratios in the uterine arteries and elevated fetal heart rates after exercise of the mother in the third trimester. S/D ratio in the umbilical artery however, was unaltered [12]. Erkkola et al. demonstrated in a series of uncomplicated pregnancies an increase in S/D ratio of the uterine arteries and the maternal blood pressure after exercise, whereas no change in S/D ratio occured in the umbilical artery. Of note, the fetal heart rate increased significantly after exercise [5].

The predictive value of maternal aerobic exercise for pregnancy-induced hypertension was studied by Hume et al. in a small series [8]. Preeclampsia developed in four patients with S/D ratios being elevated in the umbilical artery after recovery in these four patients. It was concluded, that aerobic exercise of the mother might be a valuable tool in predicting hypertensive pregnancy complications [8]. On the other hand decreased umbilical artery S/D ratios were reported after maternal exercise in the third trimester, thus indicating an improved placental circulation following exercise in healthy women [14].

Hackett et al. [7] performed a bicycle exercise test in thirty-four woman in the third trimester. Twelve pregnancies were uncomplicated, whereas 22 of the cases were complicated by small-for-gestational-age fetuses or maternal hypertension. Increase in pulsatility indices was more prominent in complicated pregnancies than in uncomplicated gestations, thus indicating an important reduction of uteroplacental blood flow by maternal exercise

in complicated pregnancies [7]. In a more recent study a fetal cerebral vasodilatation with decrease in umbilical resistance induced by submaximal maternal dynamic exercise was reported. Fetal heart rate remained unchanged in this study [2].

The present Doppler flow results of the fetal aorta and fetal cerebral vessels in normal pregnancies showed significant differences before and after exertion. The S/D ratio in the aorta increased following exertion and remained higher for a considerable time (approx. 20 minutes), although the readings did not become pathological. In IUGR fetuses the increase of S/D ratio in the fetal aorta was more important with resistance indices being in the pathological range during the time period of the test.

The S/D ratio in the cerebral artery reduced significantly following exercise and returned very quickly approximately to its initial value in AGA fetuses. In IUGR cases reduction of S/D ratio could be observed until the end of the test without return to pre-test values, thus indicating an initially decreased fetal cerebral circulation in IUGR cases after maternal exercise. Subsequently, fetal centralization (brain sparing phenomenon) occured to maintain fetal cerebral circulation.

In the present study S/D ratios of the placental vascular bed and the umbilical arteries remained unchanged throughout the test period. In three cases of IUGR we found elevated S/D ratios in the umbilical artery prior to maternal exercise. After exclusion of those cases S/D ratios in the umbilical artery was in the physiolgical range during the test in AGA and IUGR fetuses. These findings are in good accordance to results reported in the literature [3, 5, 10, 12, 16, 18, 21].

Furthermore, in the present study fetal heart rate remained unchanged after maternal exercise in AGA and IUGR fetuses. This is partly in accordance with previous studies [3, 5, 10, 12, 16, 18, 21]. Differences in study protocols might account for these differences.

In conclusion, the presented results support evidence of fetal cerebral vasodilatation leading to redistribution of fetal blood volume to the cerebrum as a physiologic answer after moderate maternal exercise during the third trimester of pregnancy. In IUGR fetuses cerebral vasodilation (brain sparing phenomenon) lasted longer than in AGA fetuses and did not return to initial levels during the test period, pointing towards an altered fetal oxygenation under these circumstances. Furthermore, our results suggest that maternal exercise does not significantly alter uterine and umbilical perfusion in AGA and IUGR pregnancies suggesting absence of change in the uterine vascular bed resistance.

These findings underline the need of close antepartal surveillance of IUGR fetuses by Doppler flow measurements in order to detect circulatory deterioration in those fetuses and to reduce long-term morbidity. This is an important and relevant task of modern perinatal medicine.

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New Methods For The Assessment of Fetal Well-Being: Fetal Oxygen Pulse Oximetry

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ABSTRACT

Background: The use of non traumatic fetal pulse oximetry - enabling the continuous monitoring of oxygen saturation - has recently been introduced in order to increase the detection rate of intrapartum asphyxia. We have tested a new pulse oximeter and sensor (to be positioned on the fetal back) with the aim to validate its efficacy and applicability.

Methods: The prospective trial included 18 term pregnancies fulfilling the criteria: an ultrasound scan in pregnancy for the confirmation of gestational age and placental location, spontaneous labor and absence of pharmacologic interference. We have used the fetal oxygen monitor OBS-500 (OB Scientific, Inc., USA), a compact pulse oxymetry device that simultaneously detected the signal of Sat O_2 and the fetal cardiac frequency by means of a flexible sensor (OBS-900) to be positioned on the back of the fetus during labor. Umbilical cord blood was obtained at birth, after double clamping of the cord before the first neonatal breath, and subsequently submitted for blood gas analysis (UBGA).

Results: The mean gestational age at birth was 39.7 ± 1.1 (37- 42 weeks), the mean neonatal weight was 3370 ± 437 g. The probe was inserted to laboring women, with a dilation between 4 and 9 cm (mean 6.0 ± 1.6 cm). In 7 cases the probe was inserted with intact membranes, under ultrasound guidance (for checking the location of the placenta). The mean umbilical artery pH was 7.28 ± 0.08, and the mean umbilical artery pO_2 15.9 ± 4.5 mmHg. The mean Sat O_2 to 5, 15 and 30 minutes before birth were 47.5%, 52.6% and 52.5%, respectively. The median of Apgar scores at 1 and 5 min was 8 and 9, respectively. From our data it emerges that a value of Sat O_2 > 50.0% corresponds to an Apgar score and to UBGA values at birth within normality.

Comment: These are preliminary results to ascertain the reliability of the method in one cluster of normal pregnancies at term. New cases are being recruited, including alterations of CTG tracing in labor, with the aim to evaluate the utility of pulse oxymetry in the decision of the modality of birth.

A number of important observations, have provided further insight into our understanding of intrapartum fetal physiology and intrapartum fetal assessment.

Regarding in-labor intrapartum surveillance, three different clinical patterns of acute fetal distress may be observed: a persistent nonreactive and "fixed" fetal heart rate (FHR) on admission to the hospital, a progressive intra-partum asphyxia manifested by a substantial rise in baseline heart rate, a loss of variability and repetitive severe variable or late decelerations, and finally, as a result of a catastrophic event, a sudden prolonged FHR deceleration to approximately 60 beats per minute lasting until delivery(1). Among all techniques tested for the evaluation of fetal hypoxia intrapartum (continuous recording of the fetal electrocardiogram or computed-assisted EFM, fetal pulse oximetry or fetal scalp sampling with immediate determination of blood gases/lactates), fetal pulse oximetry (SpO_2) has undergone a remarkable evolution since its conception over 10 years ago (2-4). An impressive development of sensors, hardware and software was necessary to convert the optical signals of reflected red and infrared light into saturation values (5). The purpose of this paper is to va-

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lidate the reliability of the method in one cluster of normal pregnancies at term with the use of a flexible sensor.

MATERIALS AND METHODS

The study was designed as an observational prospective study, guaranteeing that patient management was independent from SpO_2 readings. The saturation readings could not induce any further diagnostic means or interventions. The study was carried out in the obstetric unit of a university hospital.

Patient management was based substantially on continuous FHR monitoring. Only fetuses non showing a risk of fetal hypoxia were included in the trial. Suspicion of hypoxia during delivery, based on the occurrence of variable decelerations in the FHR tracings or meconium-stained amniotic fluid or any other circumstance requiring fetal blood sampling, were exclusion criteria such as the presence of documented uterine malformations or placenta previa. Thus, eighteen normal pregnancies were recruited on the basis of: ultrasound scans in pregnancy for the confirmation of gestational age and placental location, spontaneous labor and absence of pharmacologic interference. After an informed written consent was obtained from the laboring women, the oxisensor was positioned. We used for this study the fetal oxygen monitor OBS-500 (OB Scientific, Inc., USA), a compact pulse oxymetry device that simultaneously detects the signal of Sat O_2 and the fetal cardiac frequency by means of a flexible sensor (OBS-900) to be positioned on the back of the fetus during labor.

Total monitoring time ranged from 40 min to 4h (median 80 min). In all cases a cord blood sample was taken after double clamping of the umbilical cord before the first neonatal breath. Blood samples immediately underwent analysis in a commercial blood gas analyser (Radiometer ABL 625, Copenhagen, Denmark). The SpO_2 obtained from the blood samples were compared with the hemoximetry measurements. These couples of values were evaluated concerning mean and median of relative and absolute differences, the 95% CI and their correlation coefficients. A further aspect of evaluation focussed on the distribution of saturation in a certain time window preceding each individual fetal blood sample. This approach takes into account that SpO_2 is a method that determines the oxygen saturation levels continuously. For this purpose, the median and distribution of the saturation (SpO_2) percentiles in the chosen time frame were determined. The chosen time frames of observation were the 5, 15 and 30 min preceding the sampling.

It is well known that as the oxisensor may not continuously achieve good contact with the fetus, the amount of signal loss reduces data quality. In such instances, the 'posting time' indicates the quality of signal out-put: it describes the percentage of provided SpO_2 values during the period of time that the oxisensor was placed. The fact that the signal algorithm processes only high-quality signals and leads to reduced signal output is accepted. Data was then coded and a work-sheet created form statistical purposes.

Statistical analysis

The accuracy of SpO_2 compared with hemoximetry was calculated considering hemoximetry as the reference method. We performed for statistical differences between the groups the Wilcoxon's and Fisher's exact test. The correlation between the instantly measured saturation values of both methods was calculated by the Spearman correlation coefficient. A ROC curve (receiver operator curve) was performed in order to find a suitable limit for SpO_2 values.

RESULTS

The mean gestational age at birth was 39.7 $\pm$ 1.1 (37-42 weeks), the mean neonatal weight was 3370 $\pm$ 437 g.

The percentage signal loss rose and the posting time declined with the degree of decreasing pH in the umbilical artery. All cases underwent vaginal delivery, and an average of 10 min passed between the sensor being removed and the babies being born.

We have inserted the probe to laboring women, when the cervix showed a dilation between 4 and 9 cm (mean 6.0 $\pm$ 1.6 cm). In 7 case the probe has been inserted with intact membranes, under ultrasound guide (for diagnosisng the location of the placenta).

Data analysis focussed on the absolute and relative difference between hemoximetry and pulse oximetry of fetuses. The median disagreement between SpO_2 and umbilical artery Sat O_2 ranged between 6 and 10%. The mean umbilical artery pH was 7.28 $\pm$ 0.08, and the mean umbilical artery pO_2 15.9 $\pm$ 4.5 mmHg. The mean SpO_2 at 5, 15 and 30

minutes from birth were 47.5%, 52.6% and 52.5%, respectively. The median of Apgar scores to 1 and 5 min was 8 and 9, respectively.

We have correlated SpO_2 values to umbilical artery pH > 7.2 and Apgar score > 7 at 5 min by means of a ROC curve in order to find a significant threshold of SpO_2. From our data it emerged that a value of SpO_2 > 50.0% corresponds to an Apgar score and to UBGA values at birth within normality.

DISCUSSION

SpO_2 has been developed to a stage where it is a safe and accurate indicator of intrapartum fetal oxygenation. In general, the SpO_2 devices have been developed to a stage where it is a safe and accurate indicator of intrapartum fetal oxygenation. In general, sliding the SpO_2 sensor along the examiner's fingers and through the cervix, to lie alongside the fetal back is easy (6). The validity of our study lies on the fact that only normal pregnancies with no complications have been considered and hemoximetry from umbilical artery performed immediately. In this physiology trial we have observed that values of SpO_2 above 50.0% are related to good neonatal conditions at birth. It has been described that when fetal oxygen saturation ($FSpO_2$) values are <30%, prompt obstetric intervention is indicated, such as fetal scalp blood sampling or delivery.

Conventionally, SpO_2 may be used during labor when the electronic fetal heart rate trace is nonreassuring or when conventional monitoring is unreliable, such as with fetal arrhythmias. Reflectance pulse oximetry, which is harmless to mother and fetus (7), appears useful for fetal monitoring because it provides almost continuous information about fetal oxygenation during birth (8). Reassuring saturation and good outcome in cases of suspicious FHR traces (9) suggests that this technology provides predictive values sufficiently.

However, the disappointing experiences of the increased rate of operative deliveries after the introduction of electronic fetal monitoring in the clinical routine indicates that further evaluation of pulse oximetry is needed. We agree with the concept of a blinded-randomized data collection indispensable for the evaluation of SpO_2 in the future. Unfortunately, SpO_2 techniques may suffer the impact of artifacts (10). Possible sources of artificially low oxygen saturation readings may be meconium, which behaves in a similar manner to a red light filter (660 nm) (11). Consequently, the ratio of red/infra-red light is altered towards artificially low values. It has been published that the distance to the pressure of contraction (12) or to caput succedaneum formation (13) may lead to errors in saturation measurements. $FSpO_2$ monitoring should not form the sole basis of intrapartum fetal welfare assessment. Rather, the whole clinical picture should be considered.

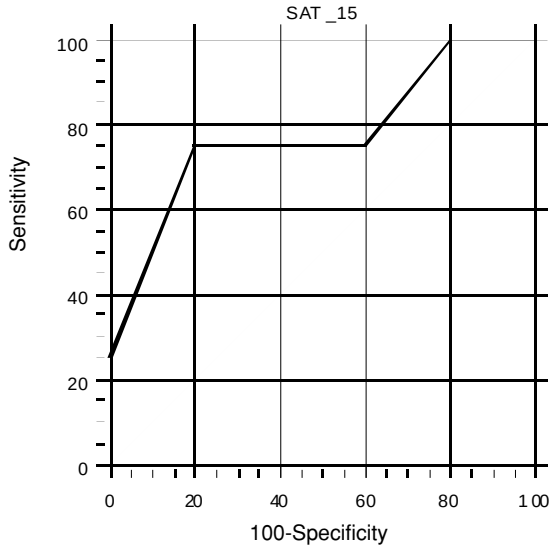

Figure 1. *ROC analysis of $FSpO_2$ readings at -15 min from delivery (SAT_15) vs. Apgar scores at 1 min >7 . Best compromise between sensitivity and specificity is $FspO_2$ = 50 %*

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