MEETING ON SURFACTANT 2015
FROM THE ELGA TO LATE PRETERM: WHICH RESPIRATORY MANAGEMENT?
Parma, Italy, June 18th 2015
AUTHOR GUIDELINES

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INDEX

Volume 86 / Supplement 1/2015

Meeting on Surfactant 2015
From the ELGA to Late preterm: which respiratory management?
Parma, Italy, June 18th 2015

5 Foreword

Delivery room management of ELBW infants in Italy

11 L. Capasso, J. Cerullo, L. Bucci, A. C. Borrelli, R. Cavazzu, F. Raimondi
Respiratory management of ELGA infants in a region of Southern Italy

16 H. Fuchs
German experience in the management of ELGAN infants

21 E. Ferrazzi, D. Casati, S. Zullino, E. Rosti
Obstetrical management of fetus with intra uterine growth restriction (IUGR) and late IUGR

24 G. Lista, A. La Verde, F. Castoldi
LISA: Surfactant administration in spontaneous breathing. Which evidence from the literature?

27 S. Mannarino, G. Corana, A. Zaroni, A.C. Codazzi, M. Pasotti, R.M. Cerbo, M. Stronati
Hemodynamic management of the preterm infant with acute respiratory failure: role of the functional echocardiography

32 S. Nobile, V.P. Carneielli
Caffeine for preterm infants: current indications and uncertainties

36 L. A. Ramenghi
Late preterm babies and the risk of neurological damage

FORECAST 2015
From the ELGA to Late preterm: which respiratory management?
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11 L. Capasso, J. Cerullo, L. Bucci, A. C. Borrelli, R. Cavazzu, F. Raimondi
Respiratory management of ELGA infants in a region of Southern Italy

16 H. Fuchs
German experience in the management of ELGAN infants

21 E. Ferrazzi, D. Casati, S. Zullino, E. Rosti
Obstetrical management of fetus with intra uterine growth restriction (IUGR) and late IUGR

24 G. Lista, A. La Verde, F. Castoldi
LISA: Surfactant administration in spontaneous breathing. Which evidence from the literature?

27 S. Mannarino, G. Corana, A. Zaroni, A.C. Codazzi, M. Pasotti, R.M. Cerbo, M. Stronati
Hemodynamic management of the preterm infant with acute respiratory failure: role of the functional echocardiography

32 S. Nobile, V.P. Carneielli
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36 L. A. Ramenghi
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This supplement of Acta Biomedica collects the Proceedings of the workshop “Dagli ELGA ai Late Preterm: quale approccio?”, held in Parma on 18-19 June 2015. The obstetrical assistance of pregnancies complicated by intrauterine growth restriction of foetus, the delivery room and NICU management of respiratory and cardiac failure, the modality of exogenous surfactant replacement by non invasive procedure (LISA) and the neurological outcome of very critical preterm babies, were the goals of our meeting with Italian and foreign speakers.

With the hope that this supplement can arouse your interest and above all support you in everyday clinical practice, we wish you all good reading.

Guest editors
Giovanni Vento
Gianluca Lista
Delivery room management of ELBW infants in Italy

Francesca Rech Morassutti1, Irene Satariano1, Nicoletta Doglioni1, Giulio Criscoli2, Francesco Cavallin1, Camilla Gizzi4, Claudio Martano1, Fabrizio Ciralli6, Flaminia Torielli7, Paolo E. Villani*, Sandra Di Fabio9, Lorenzo Quartulli10, Luigi Giannini11, Daniele Trevisanuto1, On Behalf of Neonatal Resuscitation Study Group, Italian Society of Neonatology

1 Children and Women’s Health Department, Medical School University of Padua Azienda, Padua, Italy; 2 Italian Army - Signals and Information Technology HQ - C4 Systems Integration Development, Treviso, Italy; 3 Independent Statistician, Padua, Italy; 4 Neonatal Intensive Care Unit Pediatric, Neonatal Department ‘S.Giovanni Calibita’, Fatebenefratelli Hospital, Rome, Italy; 5 Neonatal Intensive Care Unit, Pediatric Department, Medical School University of Turin, Azienda Ospedaliera OIRM-S, Torino, Italy; 6 Neonatal Intensive Care Unit, Department of Mother and Infant Science Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; 7 Neonatology Unit, University of Genova, Azienda Ospedaliera San Martino IRCCS – IST National Institute on Cancer Research, Genova, Italy; 8 Neonatal Intensive Care Unit, Maternal and Pediatric Department, Carlo Poma Hospital, Mantova, Italy; 9 Neonatal Intensive Care Unit, Department of Mother and Infant Science, ‘San Salvatore’ Hospital, L’Aquila, Italy; 10 Neonatology Unit, ‘A. Perrino’ Hospital, Brindisi, Italy; 11 Pediatric Department, Medical School University ‘La Sapienza’ Rome Azienda Ospedaliera Policlinico Umberto, Rome, Italy

Summary. In this article we evaluated the consistency of practice and the adherence to the International Guidelines in early delivery room management of ELBW infants in Italy. A polyethylene bag/wrap was used by 54 centres (55.1%). In Northern regions, one centre (2.5%) reported to use oxygen concentrations >40% to initiate positive pressure ventilation in ELBW infants. These proportions were higher in the Central (14.3%) and Southern (16.2%) areas. A T-piece device for positive pressure ventilation was widely used (77/97, 79.4%). A median of 13% (IQR: 5%–30%) of ELBW infants received chest compressions at birth in Italy. Forty-seven out of 98 (47.9%) centres declared to administer prophylactic surfactant in delivery room. Although there were geographic differences in the country, our results showed a good general adherence to the International Guidelines for Neonatal Resuscitation. (www.actabiomedica.it)

Key words: delivery room, ELBW, infants

Introduction

Approximately 5 to 10% of newborns require some assistance to begin breathing at birth. About 3% are managed with positive pressure ventilation (PPV) and <1% require extensive resuscitative measures such as intubation, chest compressions and medication. These percentages rise noticeably in preterm infants (1-3). An increasing body of evidence suggests that delivery room management of extremely low birth weight (ELBW) infants may have a direct influence on their survival and long-term morbidity (3-6). Therefore, their general outcome could be improved throughout a structured and well-coded approach starting from the first minutes of life (7-10).

In this article we evaluated the consistency of practice and the adherence to the International Guidelines for Neonatal Resuscitation in early delivery room management of ELBW infants in Italy.

Methods

The study was conducted between April and August 2012. A structured 73-item questionnaire and an accompanying introductory letter were sent by email
to the directors of the 107 Italian level III centres who provide on-site delivery, based on the Italian Society of Neonatology database. Participation was entirely voluntary.

Statistics

Categorical data are expressed as numbers and percentages, continuous data as medians and inter-quartile ranges (IQR). Statistical analysis was performed using R 2.12 language (R Development Core Team 2010. R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0).

Results

A total response rate of 92% (98/107) was obtained. There was a homogeneous representation of the country: North 40/43 (93.0%); Centre 21/21 (100%); South 37/43 (86.0%).

Characteristics of centres

Participating centres reported an overall number of 198,322 births during 2011, and of these, 1933 were ELBW infants. Northern and Central centres had a higher median of births and of ELBW infants than Southern centres.

A provider skilled in neonatal resuscitation was present in high-risk deliveries in 46% of the centres: this rate was higher in Northern (77.5%) than in Central (33.3%) and Southern (21.6%) centres.

Temperature management

The median delivery room temperature was 24°C (IQR: 22–25). Only 18 centres (20.2%) achieved a delivery room temperature over 25°C. The use of a polyethylene bag for the management of ELBW infants at birth was reported by 54 centres (55.1%), with the highest rate in Northern ones (31/40, 77.5%). Fifty-nine centres (60.2%) used a cap to cover the head of the patients at birth.

Oxygen therapy

Only a limited number of centres (10/98, 10.2%) said they used oxygen concentrations >40% to initiate resuscitation. Of these 10 centres, five said they used a 100% oxygen concentration. Almost all of these centres belonged to the Central and Southern groups. Most centres had a pulse oximeter (91/98, 92.9%) available in delivery room and used saturation targets (82/98, 83.7%).

Ventilatory support

Almost all centres used a facial mask as initial interface for PPV (95/98, 96.9%); the T-piece device was widely used (77/97, 79.4%). The use of positive end expiratory pressure (PEEP) during PPV was reported by 88 centres (89.8%). Continuous positive airway pressure (CPAP) was widely used to avoid intubation (85.4%). The oral route of intubation was chosen by most centres (61.2%), but there was a large difference in geographical subgroups. Northern centres preferred the nasal route (82.5%), whereas Central and Southern centres used the oral route (81.0% and 97.3%, respectively).

The percentage of ELBW infants intubated at birth had a median of 60% (IQR: 40%–80%), with the highest values in Central group (median 66%, IQR: 50%–75%). The percentage of ELBW infants receiving only nasal-CPAP at birth had a median of 22% (IQR: 10%–40%), with the highest values in Northern group (median 25%, IQR: 8%–45%). The percentage of ELBW infants managed without any respiratory support at birth had a median of 3% (IQR: 0%–10%).

Chest compressions and medications

A median of 13% (IQR: 5%–30%) of ELBW infants received chest compressions at birth, mostly in Central (median 18%) and Southern (median 22%) centres.

Medication was given at birth to 6% of ELBW infants (IQR: 0–17%).

Surfactant therapy

In 47/98 (47.9%) centres surfactant was routinely administered in DR. The percentage of ELBW infants treated with INSURE at birth was 0% (0%–80%).
Discussion

This study reflects the early delivery room management of ELBW infants in Italy. There were relevant differences among geographical areas in the approach to the care of ELBW infants at birth.

As the delivery room management of ELBW infants may have a direct influence on the immediate survival and also on long-term morbidity (3–6), the results of this study suggest that further efforts are needed to improve this area of care. Previous studies have reported important differences in mortality rates among neonatal units and geographical regions, irrespective of the infant’s characteristics, suggesting variable degrees of effectiveness of medical care (11,12).

In the last version of the ILCOR Committee on Neonatal Resuscitation, the body of recommendations devoted to the management of ELBW infants has been progressively increasing (1). These include strategies to prevent thermal losses, oxygen administration and ventilation. Our data show a different adherence to the guidelines in relation to the geographical area with the highest rates in Northern regions and lowest in the Southern areas. For example, the implementation of a simple practice to prevent hypothermia such as the use of polyethylene bag-wrap was limited to 37.8% of the centres in the South, in comparison with 77.5% in the Northern regions. A very similar picture was documented for other important interventions, such as the initial fraction of oxygen.

The reasons for such discordance could be due to different organizational and educational programs among the country’s regions. Although the role of continuous medical education is well-recognized, effective training programs, benchmarking and quality improvement initiatives should be further implemented and monitored. A national neonatal network including all level III Italian hospitals should be also sustained for continuous monitoring and comparison of short and long-term outcomes (13).

World Health Organization Guidelines, updated in 2003, state that environmental temperatures should be ≥25°C (14). Despite this guidance, delivery room temperatures are consistently reported to be lower than this in all healthcare settings (15,16). Also our study showed a low adherence to international guidelines that does not appear to be influenced by geographical area. The reasons that impede a widespread adoption of higher environmental temperatures remain unexplained, but perinatal teams have to consider this to be one of the greatest challenges in improving thermal care for newborn infants.

In addition, the percentages of ELBW infants who received chest compressions at birth were markedly different among the surveyed regions (median: North 5%; Centre 18%; South 22%). In the North American Vermont Oxford Network registry, which collected data on infants with birth weight of 501 to 1500 g, the proportion of those who received chest compressions was about 6% (17).

About half of the centres adopted a prophylactic strategy for surfactant administration. This approach disagree with the results of a recent meta-analysis showing a slight effect (survival without bronchopulmonary dysplasia at 36 weeks) in favor of early CPAP when compared to intubation at birth (18). However we don't know if this approach has recently changed based on the results of the most recent randomized controlled trials on this subject (18).

Overall, the results of our study are very similar to those reported in a recent survey conducted in UK: the authors found many areas of good evidence-based delivery room practice, but they identified also significant variation in delivery room resuscitation practices among neonatal services (19).

There are some limitations to this study. As we only involved the directors of the participating centres, the actual practices of individual providers may not be represented. However, a consistent part of the information obtained in this survey is related to available equipment and intent to use different practices. This study involved only tertiary units, and the approach to delivery room management of ELBW infants can be different in level I and II Italian centres. However, the majority of ELBW infants in Italy were born at tertiary units. The data on ELBW infants who were resuscitated in the centres were retrospectively collected limiting the quality of this information. Unfortunately, our questionnaire did not include questions regarding the survival rates in the surveyed centres. For this reason, we could not correlate the delivery room management with neonatal mortality.
Conclusions

Our study assess the consistency of practice and the adherence to the International Guidelines in early DR management of ELBW infants in Italy. In general, the approach to the ELBW infants at birth shows a good compliance with the International Guidelines for Neonatal Resuscitation; particular attention is devoted to temperature control, use of oxygen and less-invasive respiratory support. However, there are marked geographical differences in delivery room management of ELBW infants, and some relevant interventions are not uniformly followed by the surveyed centres. Factors contributing to such discordance remain unclear and need to be investigated in future studies. In the meantime, effective educational interventions focused on the practice of neonatal resuscitation have to be supported.

Acknowledgements

We thank the heads of the participating centres for their assistance with this survey.

References

Respiratory management of ELGA infants in a region of Southern Italy

Letizia Capasso, Julia Cerullo, Laura Bucci, Angela Carla Borrelli, Roberta Caiazzo, Francesco Raimondi

Division of Neonatology, Department of Translational Medical Sciences, Università Federico II, Naples, Italy

Summary. The distribution of births in many regions of Southern Italy is scattered among a high number of level I centers, many of which still count less than 500 deliveries per year. Campania, the region around Naples, is no exception and this excessive fragmentation results in a high number of neonatal transports, many of which for respiratory distress. In the present paper, we review three different regional peculiarities relevant to the respiratory management of extremely low gestational age babies. (www.actabiomedica.it)

Key words: respiratory management, preterm, ELGA infants

Introduction

With its 54 thousands yearly births, Campania, a southern region of Italy, accounts for 10.2% of all Italian neonates. When compared to the North and the whole country, Campania has (1):
- a gradually decreasing neonatal mortality rate (2.5‰ in 2013) that approximates the national average (2.1‰) but still significantly higher than Lombardy (1.7‰).
- a high number of level I birth centers that can assist only uncomplicated deliveries. In 2012, level I centers were 56 accounting for 37,333 neonates while at the 14 Level II/III centers 18,954 neonates were born.
- a high number of caesarean section births (regional average 60% of all deliveries)
- high number of neonatal transports (about 1,500 neonates transported each year).

Indeed, there is sufficient evidence in the literature to believe that the above variables are connected in a network of questionable efficacy and efficiency.

The aim of this paper is to review those critical features of respiratory management of preterm and particularly of extremely low gestational age babies (ELGA 23-28 weeks) that might result from the present organizational pattern.

Respiratory assistance during transport of ELGA neonates

Three dedicated neonatal transport systems are simultaneously active serving an area of 13,670.95 km² and a population close to 6 million inhabitants. The already cited scattering of births contributes to a 2.6% global transportation index (a 1% index is considered the desired standard). Our transport team (Università Federico II) operated slightly more than half the 1446 transports from January 2012 and December 2013.

During this interval, 7.2% of transported infants had a GA less than 30 weeks, a percentage that had been substantially stable across the years. When considering transported infants in need of respiratory support, out of a total 662 infants, 9% of were had a GA less than 30 weeks. This percentage was lower than the 11.8% recorded for the same class in the period 2004-2007.
As per the respiratory assistance mode during transport in the 2012-2013 period, 20 ELGA neonates received IPPV, 5 had nasal CPAP and 9 had plain oxygen therapy in the incubator.

While we detect a trend in decreasing the transports of ELGA neonates along the years, we affirm that the optimal result would be no transport at all. Low gestational age confers an additional risk of moving a baby from her/his birthplace. The low intensity of respiratory support offered to 14/34 neonates speaks in favour of relatively stable conditions and possibly short trips. One more reason to suggest birth centralization to our health policy makers.

Data from the Campania section of the Vermont Oxford Database

The latest, 2013, ELGA cohort available from the Campania section of the Vermont Oxford Network (VON) consists of 208 preterm infants between 22-29 weeks gestational age (Table 1). Their mean mortality 30.3% (IC: 22.2 – 33.3%) was higher than the Italian section of VON (Italian Neonatal Network, INN) that shows a mean mortality of 22.7% (IC: 14.3-30.6%). Considering infant characteristics at admission, 87.4% of babies are inborn (INN: 90.5%), 82.5 % received prenatal care (INN: 90.3%), chorioamnionitis rate is 13% (INN: 19.1%), maternal hypertension 21.4% (INN: 18.2%), antenatal steroids were used for 60.4% of babies (INN: 80.3%), 15.3% of babies were SGA (INN: 12.4%).

Looking at the initial resuscitation in delivery room of such small babies, in Campania the mean incidence of Apgar score < 4 at five minutes of live was 5.7% similar to the INN incidence (6.1%). Delivery room deaths were 2.3% in Campania and 1.5% in Italy. The delivery room resuscitation management in Campania included: face mask ventilation 50% (INN: 72.1%), cardiac compression 14% (INN: 9.8%), surfactant 11.3% (INN: 21.8 %), epinephrine 10.3 % (INN: 4.9%), intubation 73.4% (INN: 57%), oxygen 80.4% (INN: 85.6%), CPAP in delivery room: 13.6% (INN: 39.4%).

Respiratory distress syndrome was diagnosed in 96.2% of these babies in the Campania cohort (90.2% INN).

Mechanical ventilation was used for 88.6% of babies during hospital staying (conventional 86.2%, high frequency 46.7%) in Campania while INN data show that mechanical ventilation was used for 73.2% of babies during hospital staying (conventional 68.7%, high frequency 28.5%).

In Campania, CPAP was used for 69.5% of babies during hospital staying (but CPAP before intu-
bation only 24.8%) while in the INN cohort CPAP was applied to 77.4% babies during hospital staying (and 48.7% before intubation). High flow nasal cannula was used for 8.6% (INN: 30.3%) babies and nasal IMV/SIMV 25.7% neonates (INN: 31.6%)

Surfactant at any time during hospital staying was administered to 85.8% of babies in Campania and 74.7% in the INN. In Campania 63.8% of babies have received surfactant in the first 2 hours of life (INN: 44%).

While the incidence of pneumothorax (2.9% IC: 0-5.9%) was significantly lower than the INN data (5.2% IC: 0-8.1%), both the incidence of chronic lung disease (Campania 29.5% vs INN 26.1%) and the use of steroids for chronic lung disease (Campania 17.9% vs INN 17.3%) were comparable. Inhaled nitric oxide was used for 1% of babies in Campania and for 5% in the INN. In the year 2013, 6.1% of babies were discharged home on oxygen in Campania (8.9% for INN).

Taken together, the data suggest that ELGA infants are being born in suboptimal conditions in our region. In fact, figures from the Campania VON section (including data from 10 of 15 NICUs), show less prenatal care, much less antenatal steroids, have higher frequency of maternal hypertension and SGA compared to INN. All these conditions may contribute to explain the higher mortality rate, the more aggressive respiratory approach in the delivery room management and in the respiratory management during hospital stay of ELGA infants in Campania. Conversely, the lower figures for pneumothorax in Campania might be related to a less extensive use of N-CPAP with reduced mean airway pressure.

Strategies to improve outcomes of ELGA infants need to improve both prenatal care, and the use of pre-

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<thead>
<tr>
<th>Table 3. Characteristics of preterm infants with GA 22 - 29 weeks included in the Campania section of VON compared to the Italian group of VON (INN)- year 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VON Campania (N = 208)</strong></td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Inborn</td>
</tr>
<tr>
<td>Prenatal care</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Maternal hypertension</td>
</tr>
<tr>
<td>Antenatal steroids</td>
</tr>
<tr>
<td>Apgar score ≤4 at 5'of life</td>
</tr>
<tr>
<td>SGA</td>
</tr>
<tr>
<td>Delivery room deaths</td>
</tr>
<tr>
<td>Face mask in delivery room</td>
</tr>
<tr>
<td>Cardiac compression in delivery room</td>
</tr>
<tr>
<td>Surfactant in delivery room</td>
</tr>
<tr>
<td>Epinephrine in delivery room</td>
</tr>
<tr>
<td>Intubation in delivery room</td>
</tr>
<tr>
<td>Oxygen in delivery room</td>
</tr>
<tr>
<td>CPAP in delivery room</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>N-CPAP during hospital staying</td>
</tr>
<tr>
<td>High flow nasal cannula</td>
</tr>
<tr>
<td>Nasal IMV/SIMV</td>
</tr>
<tr>
<td>Surfactant at any time</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Chronic lung disease</td>
</tr>
<tr>
<td>Steroids for chronic lung disease</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
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<td>Babies discharged home with oxygen</td>
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natal steroids. The transportation of such immature infants should become an exceptional event by promoting “in utero” transport of all at risk of preterm birth to an adequate number of NICU beds.

At the same time, neonatologists needs to put all efforts to implement the systematic application of early non-invasive ventilation starting from the delivery room with selective surfactant administration and rapid extubation to reduce rates of mechanical ventilation, postnatal steroid therapy and ultimately chronic lung disease as recently recommended by AAP (2).

Use of Bi-level vs nasal CPAP as a respiratory support mode after extubation of VLBW and ELGA infants

Finally, we present the preliminary data from a retrospective study conducted in the NICU of the University “Federico II” in Naples, from January 2009 to December 2013. Although all VLBW infants intubated at birth were enrolled in this study, for the purpose of this paper we also extrapolated the data of ELGA infants.

The study primary aim was to compare the rate of failure of nCPAP (PEEP 4-5 cm H2O) versus bi-level (PEEP 4-5, PIP 7-8 cm H2O, it 0.7-1, rate: 10-40/min) as non-invasive respiratory support after extubation of VLBW infants with respiratory distress syndrome. Failure of n-capap and bi-level was defined as the need of more intensive respiratory support (bi-level or intubation and mechanical ventilation for the nCPAP group and intubation and mechanical ventilation for the bi-level group). The indications to switch to a higher intensity of respiratory support were: worsening of clinical signs of RDS, inability to maintain oxygen saturation between 85-95% and respiratory acidosis (pH < 7.25 and PaCO2 > 65 mmHg). Secondary outcomes were: rate of failure of nCPAP versus BiPAP within the first week from extubation, mortality, pneumothorax, PVL, BPD and ROP at discharge; 146 babies were enrolled (97 in n-capap group; 49 in bi-level group). No difference was found in the demographic variables except for birth weight and gestational age (GA): 1.071 ± 246 gr, GA 29± 1.9 in nCPAP group vs 854 ± 229, GA 27.5 ± 2.7 in bi-level group (Tab. 1). Exubation failure during the first week was more frequent in n-capap group: 25/97 (25.7%) vs 5/49 (10.2%) in bi-level group (p<0.05) (table 1). Extrapolating data for infants between 22 – 29 weeks of GA, 22/34 babies (64.7%) in n-capap group vs 5/20 (25%) in bi-level group (p<0.05) failed extubation during the first week (graph 1). No difference was found for the other outcomes for infants between 22-29 weeks of GA.

The early use of nasal ventilation has been extensively promoted in the last decade starting from delivery room resuscitation (4) and different modes of support have been proposed. Beyond the classical nCPAP, the BiPAP, i.e. two different nasal pressure during spontaneous respiration, has gained popularity. Unlike CPAP, BiPAP may generate a tidal volume that improves gas exchange. On the other hand, the success of BiPAP over n-CPAP in our setting may be related to the higher mean airway pressure delivered without difference in rate of pneumothorax. This is in keeping with the recent observation by Buzzella studying very preterm infants (23-30 weeks) that higher distending
pressures are needed post– extubation for the more immature infants (3).

In 2010 Lista in a small RCT showed that pre-term babies assigned from birth to bi-level compared with n-cpap for treatment of RDS had less need of respiratory support and fewer oxygen dependency days (5). In the same year, Ancora et al published a retrospective study showing that bi-level compared with nCPAP reduced the need for mechanical ventilation in the 7 days after Insure failure in VLBW infants (6). Recently, an Italian RCT in VLBW infants showed no statistically significant differences for bi-level compared with nSIPPV as primary treatment of RDS in the first 2 hours of life in terms of duration of ventilation and failure, suggesting that both NIV techniques are effective in the early treatment of RDS in VLBW infants (7).

Given the relatively high number of VLBW who are still mechanically ventilated, a direct comparison post extubation of nasal ventilation techniques was needed. Our data, although retrospective, contribute to fill this gap together with future larger, prospective studies.

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Correspondance:
Letizia Capasso, MD PhD,
Division of Neonatology, Department of Translational Medical Sciences, Università Federico II via Sergio Pansini 5
80131 Naples, Italy
German experience in the management of ELGAN infants

Hans Fuchs
Neonatology and Ped. Intensive Care, Center for Pediatrics, University of Freiburg, Germany

Summary. Of 680 000 infants born in Germany a year roughly 10% are preterm and 1% are very preterm. They are treated in around 150 level 1 perinatal centers and there are various credos how to best treat the ELGAN infant. However, many centers include the use of a sustained inflation for lung aeration in the standard protocol of delivery room care in Germany. As a result of the large studies on delivery room care, a trend for earlier or prophylactic surfactant in the most immature infants can be observed, however, surfactant is increasingly given in a new less invasive way called LISA. German randomized controlled trials on LISA, on permissive hypercapnia in the premature infants and a German initiated European trial on inhaled steroids have been completed and preliminary results are available. NIRS so far mostly is used for research reasons; however, the number of centers that monitor brain oxygenation for clinical reasons to guide hemodynamic management is increasing. A recent initiative was able to tremendously reduce the rate of IVH by prospective multidisciplinary surveillance. (www.actabiomedica.it)

Key words: surfactant, sustained lung inflation

Introduction

Survival of ELGA newborns (ELGAN) has increased notably over the past years, however, rates of long term sequel like bronchopulmonary dysplasia and neurologic impairment have not improved satisfyingly. Optimal respiratory and cardiovascular management in the very first hours and days of life is the mainstay to avoid such complications. However, despite the growing number of large trials there is still lack of knowledge about the best approach for the individual infant. Evidence and clinical experience have to be merged for a better outcome. Various approaches have been tested in Germany in the recent years:

Delivery room (DR) care:

In the early nineties the application of a sustained inflation to facilitate the adaptation to postnatal life was introduced into German neonatal units empirically by Wolfgang Lindner and Frank Pohlandt from Ulm (1,2). It was not until ten years later, that the rationale and benefit of this approach was studied in more detail. Prenatally the lung of the fetus is filled with lung fluid causing a high resistance of the newborns airways. te Pas et al. were able to visualize in the premature rabbit model that a long lasting inflation of more than 10 seconds is able to move the water column into the peripheral parts of the lungs, from where it is taken up into the lung interstitium (3,4). The resulting high functional residual capacity, the proposed homogenous lung aeration and the lower systemic inflammatory response compared to single breaths lung aeration in this animal model is attractive. Indeed a recent Italian study was able to proof a lower need for intubation after sustained inflation (5) and almost 30% German centers have adopted this policy (6-8). Furthermore, sustained inflations are easy to apply and effective in stabilization the infant in the DR. However, secondary outcomes from the above study, and retrospective data from a single center associate air leaks with the application of sustained inflation, therefore, caution
using this procedure may be advised (5,9). Sustained inflations are currently tested in a large international trial (SAIL-trial) (10).

**Indication of surfactant therapy and/or invasive ventilation**

Avoidance of mechanical ventilation by the use of early noninvasive support was a mainstay in the support of ELGANs in Germany. However, large scale international delivery room randomized controlled trials failed to identify significant benefits of this approach compared to the classical approach with intubation in the DR (11-14). Unexpectedly, a somewhat higher incidence of airleaks was observed with the noninvasive approach, especially if high thresholds for intubation were applied (11). Likely, this results from negative effects of late surfactant therapy in the course of moderate to severe surfactant deficiency. Would it be more advantageous to treat all infants with surfactant very early? Prophylactic surfactant therapy translated not into better outcomes (15). Some infants will not need surfactant therapy and may be treated unnecessarily. Most infants with early CPAP success without surfactant require very little or no additional oxygen for respiration (8). Identification of infants in need of surfactant identified at low FiO2 thresholds (0.3-0.4) and treatment without delay as soon as certain thresholds are met may be a key strategy to optimize respiratory outcomes.

**Mode of surfactant application**

The classic approach to deliver surfactant is intubation and surfactant therapy followed by mechanical ventilation. Attempts to deliver surfactant noninvasively by inhalation (16) or via the pharynx were hampered by low surfactant deposition. The high lipid/phospholipids content impedes nebulization. Angela Kribs from Cologne introduced in 2003 a new method to deliver surfactant through a very thin gastric tube into the trachea during spontaneous breathing (17). This approach which is now called LISA (Less Invasive Surfactant Application) recently was tested in three randomized controlled trials (RCT’s). The AVM trial in infants 26-28 weeks GA showed shorter duration of mechanical ventilation and less oxygen demands at age 28 days, however no benefit in mortality or rate of bronchopulmonary dysplasia (BPD) (18). The Take Care study compared surfactant therapy by INSURE (Intubation, Surfactant, Extubation) and LISA (19). The need for mechanical ventilation in the first 72 hours of life and the rate of BPD was significantly lower in the LISA group when compared with the InSurE group. The NINSAPP trial tested if this form of surfactant delivery is suitable for very premature infants. Infants of 23 + 0/7 to 26 + 6/7 weeks GA were randomized to LISA or surfactant therapy followed by mechanical ventilation. No difference in death or rate of BPD was found, however, the rate of intraventricular hemorrhage (IVH) was lower in the LISA group ((20) Tab. 1). LISA may in future proof to be non inferior or even superior to the classical surfactant application. Despite the sparse safety data being available, LISA is increasingly used in Germany. Data from the German neonatal network have recently been published. Between 2009 and 2012, 1103 infants <32 weeks have been treated with LISA in the network. Compared to matched controls rates of BPD, mechanical ventilation but not IVH were decreased (21).

**Gentle ventilation**

Despite new noninvasive modes to deliver surfactant up to 50% of infants may finally require invasive ventilation. Therefore, techniques to avoid ventilator induced lung injury are mandatory, if low rates of chronic lung disease or death are wanted. A potential strategy to decrease ventilatory needs and by this attenuate lung injury is to allow for a moderate level of hypercapnia. Ulrich Thome from Leibzig recently performed a German multicenter randomized controlled trial in preterm infants of 23-28 weeks GA to study the effects of permissive hypercapnia in ELGANs who

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<th>Table 1. NINSAPP trial (20)</th>
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required intubation and ventilation. A PCO2 of 55-65 mm Hg was targeted in the permissive hypercapnia group and compared to 40-50 mm Hg in the standard group. In both groups pCO2 increased in steps by 5 mm HG after the fourth day. 359 infants of 23 + 0/7 to 27 + 6/7 weeks GA were included before the trial was stopped early because of futility. Preliminary results of the interims analysis have recently been published (22, Table 2): No difference in the rate of BPD and death (36% vs 30%) were found. The rates of IVH were similar. Therefore, increasing the PCO2 targets may not be helpful and lung protective in the majority of infants. However, allowing for some more moderate degree of hypercapnia in cases of severe lung disease seems to be tolerated well without affecting the rate of intraventricular hemorrhage or other outcomes.

Inhalative steroid treatment

Early postnatal steroids attenuate lung inflammation, improve pulmonary function, facilitate extubation and decrease the rate of BPD and/or death. However, systemic steroids have been linked to adverse neurologic outcome. Therefore, high dose steroid therapy of the preterm infant needs to be restricted to the sickest infants in very severe respiratory distress. Dirk Bassler from Tübingen addressed in his large scale European randomized trial (NEUROSIS) the question, if inhaled steroids may prevent chronic lung disease without affecting neurologic outcome negatively. Preliminary results have recently been published (23;24). Inhalation of steroids significantly reduced the rate of BPD (Table 3). However, the effect was very modest and the rate of BPD or death was reduced by 6% only. Inhalation of steroids may not be the magic bullet to improve long term respiratory outcome.

Near infrared spectroscopy in the delivery room

Studies from Ulm (25) and Graz (26,27) describe the use of near infrared spectroscopy to assess regional cerebral oxygenation in the delivery room. Knowledge of the regional organ oxygenation may help to monitor adequate oxygen supply of the newborns brain which relies on arterial oxygenation, and oxygen carriers, but also on cerebral perfusion and cerebral metabolism. Percentiles of oxygen cerebral oxygenation during transition have been described in preterm and term infants. Some infants that later developed IVH had low cerebral oxygenation during and after delivery room care despite an arterial oxygen saturation within normal limits. Therefore, low cerebral blood flow very early in postnatal life may cause low tissue oxygenation which may precede IVH. Gorm Greisen from Copenhagen tested in a multicenter pilot RCT in 166 infants <28 weeks GA if cerebral oxygenation can be held within certain target ranges (55-85%) by adjusting various factors i.e. FiO2, cardiac output or hematocrit (28). Cerebral oxygenation (primary outcome) was outside the recommended range for 36.1 (9.2-79.5%) % hours compared with 81.3 (38.5-181.3) % hours in the control group. Most exiting was the fact that brain damage (secondary outcome) was strikingly lower in the NIRS group (13 vs 23% severe brain injury). Interestingly >80% of actions taken to correct cerebral oxygenation was adjustment of FiO2. NIRS, therefore, may in future help to improve outcomes and lowering the rate of IVH.

Intraventricular hemorrhage

Intraventricular hemorrhage is a major threat and the main risk factor for adverse neurologic outcome. It
affects foremost the extremely immature and sickest preterm infants. Various risk factors like immaturity, low blood pressure, sepsis have been associated with IVH, however, very little therapeutic options have arisen from this knowledge. Helmut Hummler from Ulm recently introduced an effective approach to lower rates of IVH (29). In this IVH initiative in the first step risk factors for IVH were identified by literature research. Furthermore, centers with known low rates of IVH were visited to identify potentially better practices. From this a bundle of practices were identified. Examples of these practices included: late cord clamping, no allowance of hypotension for >1h, early surfactant therapy without any delay, normocapnia, strict minimal handling policy. Adherence to these practices was henceforward in detail prospectively monitored for any preterm infant. Furthermore, each clinical course was discussed in an interdisciplinary conference of neonatologists, obstetrician and nurses on a weekly base. As a consequence overall rates of IVH decreased in infants <1500g birth weight from 22% to 10%, in infants <1000 g from 29% to 15% and in preterm infants <28 weeks from 34 to 16% (Table 4). None of the identified practices was new: It seems rather that various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed 2011; 96(5): F343-F347.


Obstetrical management of fetus with intra uterine growth restriction (IUGR) and late IUGR

Enrico Ferrazzi, Daniela Casati, Sara Zullino, Eleonora Rosti
Clinica Ostetrica e Ginecologica, Dipartimento di Scienze Biomediche e Cliniche, Università degli Studi di Milano

Summary. In this article we evaluated an important complication of pregnancy, the fetal growth restriction (IUGR). IUGR is defined as an estimated fetal weight of fetal abdominal circumference below the 10th centile measured by ultrasound according to local standards. We present the prenatal surveillance, the screening tests for late IUGR and the new diagnostic examinations, to establish the best prevention system for IUGR and late IUGR. (www.actabiomedica.it)

Key words: fetal growth restriction (IUGR); late IUGR; screening test

Introduction

An important complication of pregnancy is fetal growth restriction. A widely accepted prenatal definition of intra uterine growth restriction (IUGR) is defined as an estimated fetal weight of fetal abdominal circumference below the 10th centile measured by ultrasound according to local standards.

Perinatal mortality are increased in late preterm and term fetuses with a birth weight below the 10th population percentile. About 60% of term perinatal mortality regards children with a birth weight percentile below the 10th percentile. Yet, beyond perinatal this burden of mortality and perinatal morbidity what mostly concern clinicians are the consequences of low birth weight on future development, especially for cardiovascular, metabolic and neurological development. (‘Barker hypothesis’). It is know that adverse insults acting during intrauterine life can result in permanent changes in the physiology and metabolism of the newborn, which in turn leads to an increased risk of disease in adulthood. The “fetal origin of adult disease Hypothesis” by Barker et al identified the relationship between impaired intra-uterus growth and adult cardiovascular disease risk and death.

Fetal Programming

According to Rogers, Lillycrop and others, “the foetus appears to use the in utero environment to predict and prepare for the postnatal environment. That is, an organism alters its developmental path to produce a phenotype (observable traits, such as characteristics of behaviour, physiology, metabolism, or outward appearance) that gives it a survival or reproductive advantage in postnatal life”. This process goes by the name of “predictive adaptive response”. Epigenetics is the key to understanding the relationship between intrauterine environment and gene expression.

The placenta bears a central role in fetal programming. The placenta is the organ that the fetus uses during intrauterine life to transfer nutrients, and energetic...
substrates from maternal blood diverted in the intervillous space, to exchange gases and hormones. The determinant of these processes is trophoblast development both as an anatomic organ which accommodates maternal and fetal blood flow and a membrane exchange activity.

The aetiology of fetal growth restriction is multifactorial. The most common cause for fetal growth problems is a disturbance in the utero-placenta circulation. This disturbance develops in a slow process, but without intervention it can lead to fetal death. Insufficiency of the utero-placenta circulation is often associated with pregnancy induced hypertension and pre-eclampsia. Maternal diseases like hypertension, renal failure or pulmonary disease are associated with a higher risk of IUGR. Tobacco, drugs and alcohol are also associated with a higher risk of IUGR, where smoking is the most important negative factor. Other related factors are a low socio-economic status, stress, poor diet and maternal age (very young women and a high maternal age). Foetuses with congenital or genetic abnormalities are also at a higher risk for IUGR. The most important risk factors are medical diseases; especially hypertensive disorders, smoking and complications in a previous pregnancy.

Prenatal Surveillance

Antepartum fetal surveillance is essential in managing these pregnancies and timely recognition of complications. Term, growth restricted foetuses present the obstetrician with at least two difficulties. Firstly they are difficult to identify. After identification of the small fetus, the second challenge concerns, the distinction between pathologically small foetuses, most likely accompanied by a suboptimal placental function, and constitutional healthy small foetuses. Such a distinction is difficult, since most assessment tools fail during the term period. Umbilical artery Doppler fails in recognizing the fetus with true growth restriction at near term or term age. Similarly, Doppler velocimetry of the uterine arteries although more sensitive in the identification of the risk of small placentas is still just a proxy of the real maternal vascular supply line to the placenta. In spite of these limitations ultrasound measurements of the abdominal circumference and Uterine Doppler velocimetry could be considered for screening late IUGR foetuses

Screening tests for late IUGR

1. Cross sectional Abdominal circumference measurement below the 10th percentile does not represent growth, yet it represents a robust reproducible screening test between 35+0 and 37+6 wks’gestation. Intrauterine death due to growth restriction before 37+6 weeks is an exceptional event and therefore this window of gestation represents a proper timing of screening for abnormal fetal growth before delivery.

2. Uterine Doppler velocimetry in late gestation might identify foetuses at risk of IUGR due to placental vascular insufficiency, that might be lost by fetal biometry.

When recognized, another challenge is formed by limited therapeutical options. The only possible intervention consists of adequately timing of birth. Optimal timing of elective delivery is difficult in pregnancies complicated by intra uterine growth restriction due to lack of adequate diagnostic tools. The importance of being able to identify foetuses at risk resides in the possibility to target interventions with potential adverse effects if used too liberally. This has been shown by a recent large randomized trial in which an unselected population of term foetuses with an estimated fetal weight below the 10th percentile were randomized between immediate induction of labor or expectant management. The incidence of adverse outcomes did not differ between both groups. In other words, too many constitutionally small foetuses were exposed to an unnecessary intervention with risks of complications obscuring the possible gain of early intervention in foetuses at real risk.

Many parameters have been evaluated to distinguish between constitutionally small and pathologically growth restricted foetuses with little result so far. Doppler evaluation of flow patterns in the umbilical artery are used routinely in preterm growth restricted foetuses but are normal in most cases in term small-for-gestational-age foetuses. This due to the fact that a high placental resistance occurs only when more than 1/3rd of placenta function is deficient. Oligohydramnios is not specific enough. Abnormal fetal heart rate
patterns can reliably identify fetal distress but are a late sign of impairment. Monitoring of fetal movements is subjective and reduced movements are generally also a late sign of impairment.

Recently a number of new diagnostics tools have been described in small case series, which have potential in the early recognition of the term IUGR fetus at risk for adverse neonatal outcome:

**New diagnostic examinations**

1. Blood flow volume in the uterine artery assessed with Doppler ultrasound seem to be more sensitive than just the arterial Doppler waveform.
2. Blood flow volume in the umbilical vein can sort out minor reduction in nutritional function of the placenta notwithstanding normal Umbilical artery waveform.
3. PGF/sFlit-1 might be a useful biomarker of placental vascular dysfunction and add its predictive value in identifying small foetuses accompanied by dysfunctional placenta.
4. The cerebro-placental ratio (CPR) defined as the ratio between the pulsatility index measured in these arteries has been shown to be related to MRI abnormalities and abnormal neonatal neurobehavioral development. In fact, subtle opposite changes in flow patterns of umbilical arteries and middle cerebral artery might also identify the fetus at risk.
5. Computerized CTG is of clinical relevance in identifying abnormal variability in severe growth restricted foetuses, yet short term variability and an exact identification of small and large accelerations might contribute to identify subtle changes in fetal adaptation to limited placental resources.
6. Advanced analysis of fetal heart rate patterns specifically assessing changes in the autonomous regulation of fetal heart rate may also identify the IUGR fetus at increased risk. Early signs of hypoxemia are found in changes in the autonomous regulation of the fetal heart rate. This can be assessed by relatively new promising methods; spectral analysis or phase rectified signal averaging (PRSA) of the fetal heart rate, measured by electromyography. Both methods are more specific than conventional analysis in identifying hypoxemia during labour or growth restriction ante partum. Research from Munich, Utrecht, and from our group has shown abnormalities in about 30% of SGA foetuses, compared to only 5-8% with conventional computer analysis. Most of these cases were preterm and correlations with neonatal outcome have not yet been studied.

The challenge is to find combinations amongst these monitoring modalities that will identify and monitor late IUGR, in such a way that targeted intervention studies can be performed in order to optimize diagnosis and prevent long term cardiovascular and metabolic sequelae in this large subset of foetuses.

**Conclusions**

It is clear from this brief analysis that late IUGR remains a major challenge in perinatal medicine. Unfortunately the italian ultrasound screening protocol for IUGR at 30-32 weeks of gestation represents a major problem, too late for early severe IUGR, too early for late IUGR, a total useless misleading waste of money.

Whereas the TRUFFLE protocol represents a clear cut monitoring system for early IUGR, further studies are still to be performed in order to define the optimal screening and monitoring methods for late IUGR.

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Correspondance:
Enrico Ferrazzi, MD
Dir. S.C. di Ostetricia e Ginecologia
Ospedale dei Bambini “V. Buzzi”
ICP - Dip. di Scienze Cliniche - UNIMI
E-mail: enrico.ferrazzi@icp.mi.it
LISA: Surfactant administration in spontaneous breathing. Which evidence from the literature?

**G. Lista, A. La Verde, F. Castoldi**
NICU «V. Buzzi» Ospedale dei Bambini, ICP, Milan, Italy

**Summary.** Recent human and animal studies demonstrated that surfactant can be delivered intratracheally without traditional intubation and bagging, but using a fine catheter inserted into the trachea of spontaneously breathing preterm infants on CPAP. This strategy, known as LISA (less invasive surfactant administration) or MIST (minimal invasive surfactant therapy), seems to reduce failure of non-invasive respiratory approach. Avoiding mechanical ventilation and manual inflation it is possible to reduce lung injury due to baro-volutrauma. Moreover leaving the infants supported by N-CPAP during the maneuver, it is possible to reduce the risk of lung derecruitment. Further studies are needed to confirm the promising effects due to this strategy to deliver surfactant. (www.actabiomedica.it)

**Key words:** surfactant, spontaneous breathing, preterm infants, RDS

**Introduction**

Surfactant administration is a well recognized management for respiratory distress syndrome (RDS) (1); N-CPAP and Non Invasive Ventilation (NIV) are often used to reduce the occurrence of mechanical ventilation (2-3) and so to minimize the risk of lung injury and the evolution towards bronchopulmonary dysplasia (BPD).

INSURE procedure (transient intubation for surfactant administration, followed by a brief ventilation with final extubation to restore the non-invasive respiratory support in spontaneous breathing preterm infants) used in some recent RCTs (4-6), it has been recognized to reduce the need of mechanical ventilation (MV) (7).

Anyway in order to reduce the potential risk of tracheal intubation and lung injury due to the ventilation even if for a short period during INSURE procedure, a new method to give exogenous surfactant without tracheal intubation and MV has been studied since 2001; this method leaves the baby spontaneously breathing on CPAP during the procedure. The glottis is visualized with the laryngoscope and the surfactant is introduced in the trachea using different thin catheters. The procedure is called LISA (less invasive surfactant administration) or MIST (minimal invasive surfactant therapy).

In literature many important experiences are described about the use of this “less or minimal” invasive modality for surfactant replacement therapy in spontaneously breathing preterm infants on non-invasive respiratory support.

In Germany, Angela Kribs documented as a single center experience that this procedure is feasible with rare early complications and able to reduce the rate of N-CPAP failure (from 46% to 25%) with an increased survival rate (from 76% to 90%) and survival without BPD (from 65% to 80%) (8-11).

After this single center experience, in Germany was planned the “AMV trial” (Avoiding Mechanical Ventilation): a RCT (19 NICUs) that enrolled 220 preterm infants (26.0-28.6 wks’GA) who were randomized to standard treatment (INSURE) or to inter-
Surfactant in spontaneous breathing: evidence from the literature

The LISA group showed significantly fewer median days on mechanical ventilation, (0 days. IQR 0–3 vs 2 days, 0–5) and a lower need for oxygen supplementation at 28 days (30 infants [30%] vs 49 infants [45%], p=0.032) compared with the INSURE group. The thin catheter used (diameter 5 french) was always inserted with the Magill forceps. They recorded no differences between groups in terms of mortality (7 deaths in the intervention group vs 5 in the standard treatment group) and serious adverse events (21 vs 28 respectively) (12).

In 2014 using the data from the German Neonatal Network (GNN) each infant (below 32 wks'GA) receiving LISA (between 2009 and 2012) was matched with one infant not treated with LISA. All the patients (1103 neonates in each group) were analyzed about their respiratory outcomes. LISA infants had lower rates of mechanical ventilation (41% versus 62%, p < 0.001), postnatal dexamethasone treatment (2.5% versus 7%, p < 0.001), BPD (12% versus 18%, p = 0.001) and BPD or death (14% versus 21%, p < 0.001) than the controls.(13)

In Australia, Dargaville (14) planned a non-randomised feasibility study on two groups of spontaneously breathing babies on N-CPAP (25-28 wks' GA (n= 11) and 29-34 wks'GA (n=14) who received the “minimal invasive surfactant therapy” (MIST). Without any premedication, a 5 F vascular catheter was inserted through the vocal cords under direct vision. Porcine surfactant (~100 mg/kg) was then instilled, followed by reinition of N-CPAP. The catheter was prepared by marking a point indicating the desired depth of insertion beyond the vocal cords with a marker pen (the point was different according to different GA). In all cases, surfactant was successfully administered (in 10–20 seconds) and N-CPAP re-established with reduction in FiO2 and pressure. An open feasibility study for the use of MIST was then organized (15), including stable preterm neonates (61 neonates of 25–32 wks' GA) with a N-CPAP level above 7 cmH20 and need of FiO2 > 0.3–0.35 (according to GA). In this case the MIST procedure was given maintaining the infant with the CPAP prongs in situ and the administration of surfactant lasted about 15–30 seconds. Oxygenation improved rapidly after MIST procedure in all patients. Rates of pneumothorax, BPD and other major morbidities were not substantially different between the MIST group and their respective controls managed with INSURE procedure. Duration of respiratory support was similar between MIST and control groups, but the length of oxygen therapy was lower in MIST group.

The LISA procedure was tested in a spontaneous breathing preterm lamb model. Preterm lambs (n = 12) of 133–134 days of gestational age were randomized to receive surfactant (as a bolus in 30–60 seconds) while spontaneously breathing (using a 5F, flexible, sterile nasogastric tube for the procedure called TAKE CARE procedure) or with INSURE procedure (100 neonates per group). No sedation was used. Mean duration of both N-CPAP and MV were significantly shorter in the Take Care group (P values .006 and .002, respectively). BPD rate was significantly lower in Take Care group (relative risk –0.27, 95% confidence interval –0.1 to –0.72)(16).

The LISA procedure was tested in a spontaneous breathing preterm lamb model. Preterm lambs (n = 12) of 133–134 days of gestational age were randomized to receive : (i) continuous positive airway pressure (CPAP) only, (ii) CPAP + LISA, and (iii) intubation and mechanical ventilation with surfactant administration. Surfactant was labeled with samarium oxide. During the next 180 min after randomization, blood gas analyses were performed. Postmortem, lungs were removed and surfactant distribution was assessed, and pressure–volume curves were performed. LISA improved oxygenation, similar to conventional surfactant application techniques, despite lower surfactant deposition (at the right upper lobe) and lung compliance. (17).

Conclusions

Surfactant administration to spontaneously breathing preterm infants (LISA or MIST procedure) seem to be safe, well tolerated and associated with reduced NIV failure and less need of mechanical ventilation.

Actually there is not a universal consensus about the best choice of the catheter to use for the procedure,
the length of manoeuvre, the need for Magill forceps and for an eventual pre-medication, the safety for all the spontaneously breathing preterm infants in non-invasive respiratory support, independently from the GA and birth weight, whenever the surfactant administration is considered necessary.

Moreover it could be important to evaluate (e.g. in animal experiment) if this procedure could be enhanced by a preliminary maneuver to recruit the lungs and so to allow a better distribution of surfactant in course of spontaneous breathing only supported by N-CPAP.

Anyway, even if BPD is a multifactorial disease, LISA/MIST procedure for surfactant administration because seems to improve short term respiratory outcomes (e.g. need of mechanical ventilation and length of respiratory support) could reduce the risk of lung injury and so the evolution towards BPD. More larger RCT are needed to confirm this hypothesis.

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Correspondance:
Gianluca Lista, MD
NICU - “V.Buzzi” Ospedale dei Bambini
Azienda ICP, Milano-Italy
Tel./Fax (39) (02) 57995346
E-mail: g.lista@icp.mi.it
Hemodynamic management of the preterm infant with acute respiratory failure: role of the functional echocardiography

S. Mannarino¹, G. Corana¹, A. Zaroli², A.C. Codazzi², M. Pasotti², R.M. Cerbo², M. Stronati²

¹ Pediatric Cardiology, Department of Pediatrics; ² Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Summary. The functional echocardiography is a useful tool to evaluate the hemodynamic status of preterm infants, often needing a respiratory support during the first critical days of life. In NICU it can be helpful either for the clinical monitoring or the therapeutic management and the use of this technique can potentially improve short-term outcome of preterm infants. (www.actabiomedica.it)

Key words: functional echocardiography, hemodynamic status, preterm infants

Introduction

The term “functional echocardiography” describes the use of echocardiography as an adjunct in the clinical assessment of the hemodynamic status in newborn infants. Usually pediatric cardiologists perform echocardiographic studies in the Neonatal Intensive Care Units (NICU) to diagnose or to monitor congenital heart diseases (CHD) and to screen for patent ductus arteriosus (PDA). However, neonatologists frequently have to deal with the management of hemodynamically instable preterm neonates and only a small proportion of these neonates may present an undiagnosed CHD in this setting (1-3).

The assessment of ventilated preterm infants with cardiovascular compromise is one of the main challenges for neonatologists and, at present, continuous non-invasive real-time monitoring of cardiac function and hemodynamic status is not routinely available (4).

The cardiovascular compromise in these patients is the result of prenatal and postnatal factors that adversely affect organ perfusion during the period of postnatal transition, especially in the presence of immature myocardium (5, 6).

Clinical signs of poor perfusion are useful but not sufficient to evaluate the cardiovascular status and there is a poor relationship between blood pressure (BP) and systemic blood flow (SBF), particularly in the context of highly variable systemic vascular resistances (SVRs) (7-9).

The functional echocardiography satisfies the need to obtain real-time information by a non-invasive and easily reproducible method that can provide data useful for the clinical decision-making. This technique, performed by adequately trained intensivists, can change the clinical management and potentially improves short-term outcome (3, 10, 11). At present no data exist on long-term outcome.

In order to get reliable echocardiographic parameters it is necessary to repeat measurements using more than one method, to minimize inter- and intra-observer variability, to achieve good quality of images also in the presence of hyperinflated lungs in ventilated preterm infants.
Hemodynamic compromise

Prematurity increases the need for invasive and non-invasive respiratory support and infants with severe respiratory distress syndrome (RDS) may have lower BP than infants with less severe or without RDS (12, 13). Different factors, often acting together, influence the relationship between BP and SBF:

1) The increased airway pressure depending on the type of invasive ventilation (conventional or high frequency ventilation) and the use of positive-pressure ventilation influence SBF. Many authors report a negative correlation between the mean airway pressure in mechanical ventilated preterm infants and the BP. High ventilation pressures can reduce the preload by reducing systemic and/or pulmonary venous return, while direct compression of cardiac chambers increases the afterload and reduces the stroke volume. So mechanical ventilation alters intrathoracic pressure and thereby affects the cardiovascular system, mainly the right ventricle (RV); however, considering an in-series circulation, a reduction of the RV output also reduces that of the left ventricle (LV) (14, 15, 16). In addition, a too high positive end-expiratory pressure (PEEP) and, presumably, the resultant hyperinflation of the lungs may induce the release of plasmatic factors having negative inotropic action (17). Current data show a decreased necessity of mechanical ventilation by using early nasal continuous positive airway pressure (nCPAP) with early surfactant administration. The INSURE method (Intubation - Surfactant - Extubation) followed by positioning nCPAP potentially can reduce the incidence of hypotension and decreased perfusion in very low birth weight (VLBW) infants (18).

2) Blood losses may further reduce the preload; a delayed cord clamping (DCC) reduces the risk of hypovolemia (19).

3) There is a close relationship between SVRs and cardiac output; different factors affect SVRs such as carbon dioxide level, unbalance of vasoactive substances, inadequate immature sympathoadrenal system and sepsis. Furthermore, during the first hours of life (very vulnerable status) the enhanced SVRs can significantly decrease SBF with consequent poor neonatal outcome (20, 21).

4) PDA, which exposes LV to the combined pulmonary and systemic vascular resistances, plays an important role in determining hemodynamic instability when it is significant (22, 23).

5) The role of myocardial dysfunction as a primary cause of hypotension in severely asphyxiated preterm infants is well-documented (24). Transient dysfunction is usually the result of an unsatisfactory response of immature myocardium to the suddenly increased left afterload and can play a role in the development of a low flow in the superior vena cava (SVC) (25).

Functional echocardiography

The functional echocardiography allows the evaluation of different useful parameters: blood flow measurements; measurements of myocardial performance, ductal and atrial shunting, pulmonary artery pressure (PAP). The complex relationship among these parameters in the unique condition of the transitional circulation implies a complete evaluation of all these measurements for the correct assessment of the preterm infants’ hemodynamic status.

- Blood flow measurements

Three main measures are necessary to estimate stroke volume: mean flow velocity, cross-sectional vessel area and heart rate. To minimize measurement errors, the flow must be laminar and sampled at an angle < 20° while the vessel diameter must be achieved when the ultrasound beam hits the vessel at 90°. It is important to consider that the LV output can be used to estimate SBF only in the absence of ductal shunt, otherwise it becomes an index of pulmonary blood flow as the sum of the SBF and the left to right shunt across the duct. In this situation, the RV output is a better measure of the SBF. There is a good correlation between RV and LV out-
put in the absence of atrial and ductal shunts, but a large left to right shunt overestimates RV output (4). The SVC flow is independent of shunts and represents the portion of SBF for the brain and the upper body. Its measurements is technically difficult and in newborns breathing spontaneously requires to average from 10 cardiac cycles (4). A low SVC flow relates to a poor neurological outcome (26).

• Measurements of myocardial performance
  The simplest measure of the LV systolic function is the fractional shortening (FS), commonly derived from a M-mode study. Unfortunately, during transitional circulation, the individual fall time of pulmonary vascular resistances (PVRs) and the close interdependence of the two ventricles affect the septal and LV anterior wall motion, making the FS a not very reliable measure. Other methods to evaluate myocardial performance have been suggested (4, 27). An important limit of the estimation of the global systolic function is the impossibility to differentiate how each of the three major components (preload, afterload and intrinsic contractility) affects the changes. The estimation of the velocity of circumferential fiber shortening (VCF) and the relationship between VCF and wall stress (WS) (28) are helpful, but not so easy to be performed in clinical practice. In future, the functional study of the immature heart with the tissue Doppler technique could provide many advantages.

• PDA
  The echocardiographic assessment of PDA includes different parameters: ductal diameter, transdual flow pattern, mean left pulmonary artery (LPA) velocity, signs of left heart volume and pressure overload (LA/Ao ratio, mitral regurgitation jet, E/A ratio, isovolumic relaxation time IVRT), arterial diastolic reverse flow in the normal end-organ vessels (cerebral, mesenteric, and renal arteries). The risk of hemodynamically significant PDA increases with low gestational age and, although it has been linked to important neonatal morbidities (early pulmonary hemorrhage, chronic lung disease and neonatal necrotizing enterocolitis), there is little evidence that its treatment improves either short-term or long-term outcomes (22, 23, 29). However, echocardiographic criteria such as ductal internal diameter greater than 1.5 mm, LA/Ao greater than 1.5, absent or retrograde diastolic flow in postductal descending aorta, increased mean LPA velocity, in association with demonstrated adverse clinical effects, address to PDA closure (30, 31).

• Atrial shunting
  In preterm babies left-to-right atrial shunt can be both significant and quite persistent; atrial shunting is determined predominantly by RV filling or diastolic pressure. It can contribute to increase pulmonary blood flow and overestimates the SBF in the presence of PDA. A bidirectional shunt alone is not a marker of pulmonary hypertension; an exclusive right-to-left atrial shunting is rare and should be investigated for CHD (4).

• PAP
  PAP echocardiographic estimation is obtained by measuring tricuspid regurgitation jet or ductal shunt and the direction of atrial shunt (4). When pulmonary hypertension (usually a problem of term or near term newborn) affects preterm neonates, excluding a CHD or a secondary cause such as pulmonary embolism is mandatory.

Conclusions

Currently there is agreement to perform an echocardiography during the first 12 hours of life in extremely low-gestational-age (ELGA) infants and in the preterm neonates born after 27 weeks of GA with respiratory compromise, to monitor the vulnerable transition period. This evaluation must include:

a) the measurement of SBF with a simple method: if atrial shunt is not very large, maximum velocity in the main pulmonary artery (MPA) greater than 0.45 m/sec most likely excludes low SBF; on the contrary, when maximum velocity in MPA is lower than <0.45 m/sec, it is necessary to estimate the RV output and to evaluate the SVC flow (32);
b) the ductus arteriosus assessment: early constriction or patency, considering that significant left to right shunt is often clinically silent during the first hours or days of life.

Further echocardiographic assessments are necessary when there is the suspicion of a circulatory compromise or, longitudinally, to follow the effectiveness of some therapeutic decisions. A full assessment of ductal patency, the measurement of LV and RV output and the indirect (visual) and/or direct (FS, VCF, tissue doppler) measurement of the myocardial function can better address clinical decision.

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Correspondence:
Mannarino Savina
Pediatric Cardiology, Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, Viale C. Golgi 19, 27100 Pavia, Italy
Tel. + 39 0382 502915
E-mail: savinamannarino@smatteo.pv.it
Caffeine for preterm infants: current indications and uncertainties

S. Nobile, V.P. Carnielli
Neonatology Unit, Salesi Children’s Hospital, Ancona (Italy)

Summary. Caffeine is one of the most commonly used therapies in Neonatology, with different indications such as the treatment of apnea and the prevention of extubation failure and bronchopulmonary dysplasia. However, there are still uncertainties regarding effects on central nervous system development, time of discontinuation and dosing of the drug. (www.actabiomedica.it)

Key words: caffeine, preterm infant, apnea, bronchopulmonary dysplasia

Background

Caffeine is one of the most commonly used therapies in Neonatology, with different indications such as the prevention/treatment of apnea and the prevention of extubation failure. (1,2) Recent studies showed that caffeine is also effective in reducing bronchopulmonary dysplasia (BPD) rates (3-7).

Nearly all very low birth weight infants (VLBW; <1,500 g) experience apnea due to brainstem and peripheral chemoreceptor immaturity; in addition, pathologic conditions such as sepsis, respiratory failure, intracranial hemorrhage, and seizures may increase the number and severity of apnea events (3).

BPD is another common complication of prematurity, which occurs in over 40% of VLBW infants. Neonates with BPD are at high risk of long-term lung disease, adverse neurodevelopmental outcomes and hospitalization in the first year of life. Few safe and effective therapies are available to prevent the disease, including caffeine (4).

Methods

We performed a literature search on Pubmed and selected the most relevant studies about pharmacology and clinical use of caffeine among preterm infants.

Results

Pharmacology

Caffeine is a methylxanthine acting as a non-specific inhibitor of 2 (A1 and A2a) of the 4 known adenosine receptors A1, A2a, A2b and A3. Adenosine is a purine nucleoside produced in human tissues, including the brain, whose levels increase rapidly with inflammation (1). Adenosine preserves brain ATP levels and protects brain cells from energy failure and cell death during experimental hypoxia and ischemia in a variety of animal models.

Caffeine is thought to act by increasing central respiratory drive and by lowering the threshold of response to hypercarbia, as well as by stimulating diaphragmatic contractility and preventing diaphragmatic fatigue. Other suggested mechanisms include diuretic effect, increased cardiac output and blood pressure, improvement in overall pulmonary mechanics, resulting in a reduction of endotracheal ventilation and protection against associated lung injury (8).

Most studies reported intravenous administration of caffeine. The systemic absorption of caffeine from the gastrointestinal tract has been found to be complete in preterm infants (9). Therefore, caffeine administration can be simplified because dosing can...
be switched between orogastric and intravenous routes as required. The mean absorption half-life is about 30 minutes.

Caffeine is very rapidly distributed, with a half-life of < 10 minutes. Caffeine clearance has been described as a function of body weight and postnatal age (which is in turn correlated with renal and hepatic development). Preterm infants tolerate caffeine very well, even at serum concentrations of 70 mg/L or above. Lee et al reported a very long caffeine half-life of 86 to 277 hours, much higher compared with 5 hours in adults (8). The large majority of the drug is cleared by the kidneys. Distribution reflects a partitioning of caffeine into the relatively larger extracellular fluid volume of the newborn, especially in skeletal muscle.

The binding to serum albumin is low (35%) for caffeine concentrations up to 20 mg/L. Indeed, it is likely that the protein binding of caffeine in premature neonates is linear to at least 70 mg/L, as pointed out by Lee and colleagues (8).

Natarajan et al. 2007 suggested that routine monitoring of plasma concentrations of caffeine is unnecessary, even in VLBW infants with renal or hepatic dysfunction or after prolonged use, because the vast majority of patients achieve blood concentrations in the range of 5 to 20 mg/L (10). In the subgroup of infants who do not show a clinical response to standard doses of caffeine, higher plasma levels may be targeted, and monitoring of plasma levels may be prudent. Pharmacokinetic studies in premature neonates showed that the half-life of caffeine is prolonged to 102.9 ± 17.9 hours and remains prolonged for as long as 38 weeks’ gestation. The transition to adult levels of elimination occurs at 3 to 4½ months. Other factors such as cholestasis and breastfeeding seem to further prolong the half-life of caffeine.

The recommended standard dosing for caffeine citrate is 20 to 40 mg/kg (loading dose) followed by 5 to 8 mg/kg per day as maintenance. Larger maintenance doses up to 20 mg/kg day in the perextubation period have shown higher rates of successful extubation, without adverse events in the first year of life (2).

Reported adverse events during caffeine therapy are tachycardia, central stimulation, and alimentary tract toxicity; however, caffeine is a relatively safe drug, and even at the maximum observed concentration of approximately 80 mg/L, it has few significant acute adverse effects in preterm infants, and no apparent detrimental developmental outcomes up to at least 1 year of age after administration during the perextubation period (2).

There is uncertainty on the precise desired plasma concentration and its correlation with efficacy, as clinically effective plasma concentrations vary over a wide range of 5 to 50 mg/L. Although a decrease in apnea and increase in respiratory drive is known at plasma concentrations as low as 2.9 and 4 mg/L, optimal effect is at 10 mg/L. Higher doses and caffeine levels have been targeted with some benefit and no adverse effects. However, a recent study showed that administering intravenous loading dose 80 mg/kg compared to 20 mg/kg in the first 24 hours of life was associated with higher incidence of cerebellar injury with subsequent alterations in early motor performance (11).

Clinical studies

Caffeine has been increasingly used from the 70’s to treat apnea, prevent extubation failure and BPD. Given the concerns for potential adverse events that emerged from in vitro studies (brain toxicity in hypoxia models), large trials have been conducted in order to evaluate short- and long-term safety and efficacy of caffeine (3,12,13).

The CAP trial, an international, multicenter, placebo-controlled randomized trial conducted on preterm infants (with birth weight below 1250 grams) showed that caffeine significantly reduced the frequency of BPD (36.3 vs 46.9% for placebo). The rates of death before the first discharge home, ultrasonographic signs of brain injury, and necrotizing enterocolitis did not differ significantly between the two groups (3).

Other studies confirmed the decreased neonatal morbidity (in terms of death, BPD, PDA, duration of endotracheal intubation) with early (before 3 days of life) versus late initiation of therapy (4-7).

In a later follow-up study from the CAP trial,(12) caffeine compared to placebo significantly improved the rate of survival without neurodevelopmental disability at a corrected age of 18 to 21
months (59.8% vs. 53.8%, odds ratio 0.77; 95% confidence interval 0.64 to 0.93; P = 0.008). There was no significant difference between the two groups in the rate of death before the age of 18 months. The rates of deafness and bilateral blindness were low and likewise not significantly different between the two groups. Treatment with caffeine as compared with placebo significantly reduced the incidence of cerebral palsy (4.4% vs. 7.3%; odds ratio 0.58; 95% CI 0.39 to 0.87; P = 0.009) and of cognitive delay (33.8% vs. 38.3%; odds ratio 0.81; 95% CI 0.66 to 0.99; P = 0.04). Nearly one-half of the neuroprotective effect of caffeine at 18 months could be explained by the earlier discontinuation of positive airway pressure in infants assigned to caffeine. Another possibility is that caffeine has antioxidant capacity, as suggested by a recent experimental study on mice reporting that caffeine exerts protection for neonatal neurons exposed to high oxygen (14).

In a subsequent follow-up study of the CAP trial in which infants were evaluated at 5 years of age, Schmidt et al. reported that there was no difference between children treated with caffeine and those who received placebo with regard to a combined outcome of death or survival with 1 or more of the following: motor impairment, cognitive impairment, behavioral problems, poor general health, severe hearing loss and bilateral blindness (13).

Regarding the optimal time of discontinuation of caffeine therapy, a recent study pointed out that extending caffeine treatment to 40 weeks’ post-menstrual age decreases intermittent hypoxia events (SatO2 <90%) compared to earlier discontinuation (34 to 37 weeks PMA); thus, prolonged administration might improve neurodevelopmental outcome among preterm infants (15).

Discussion

Caffeine appears to be a safe and effective therapy for apnea of prematurity, prevention of BPD and extubation failure in preterm infants (i.e. born <29 weeks’ gestational age) who require ventilatory support or present apnea events. More clinical research is needed to confirm potential neuroprotective properties of the drug and to clarify the optimal dosing and time to discontinuation of therapy.

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Correspondance:
Stefano Nobile, MD
Neonatology Unit
Salesi Children’s Hospital
Ancona, Italy
E-mail: stefano.nobile@ospedaliriuniti.marche.it
Late preterm babies and the risk of neurological damage

Luca A. Ramenghi
Neonatal Intensive Care Unit, Istituto Giannina Gaslini IRCCS, Genova, Italy

Summary. Late preterm infants (born between 34+0 and 36+6 weeks gestation) account for the recent striking increase in premature birth and they carry a higher vulnerability to suffer brain insults compared to term infants. These babies can develop any kind of known brain lesions including those affecting the most premature babies (i.e. intraventricular haemorrhage) and lesions affecting more typically term babies like asphyxia and stroke. In other words there is not a specific brain lesion characterizing this gestational age group, and there is not a specific maturational landmark although “subplate neurons” are suppose to ultimate their connectivity in this period and the cortical volume is significantly increasing. In addition we should not forget the possibility that “late preterm babies” may present neurological clinical impairments in the absence of recognized morphological brain lesions even with the use of highly sophisticated MR imaging techniques. For these reasons a wider use of more sophisticated neuro radiological studies is not sufficient to better understand why some studies highlight that the risk of developmental delay or disability can reach 36% higher among late preterm infants compared with term infants. We believe we should improve also our skills to identify even those very subtle clinical signs of impairment deserving further investigations although we often admit these babies in the normal post natal nurseries where clinical observation cannot be so appropriate. (www.actabiomedica.it)

Key words: late preterm, neonatal brain, preterm brain

Introduction

Late preterm infants (defined as babies born between 34+0 and 36+6 weeks gestation) have been grouped together only because they are the most represented premature infants (about 72% of preterm births) in the developed countries, reaching 7-8% of total live-borns, and they account for the striking increase in premature birth which occurred in the last two decades (1). There is not a peculiar common pathway to develop certain disease characterizing this peculiar gestational age group, especially for cerebral lesions as between 34 and 36 weeks of gestation there is a continuum between the most important prematurity and what we intend for term babies.

The higher vulnerability of late preterm infants to develop diseases in the early neonatal period, compared to term babies, is well known. Mortality rate shows a 3-fold increase compared to term born controls and morbidity rates approximately doubles for each additional gestational week earlier than 38 weeks (1). Short term morbidities of late preterm infants include temperature instability, respiratory distress syndrome, excessive weight loss and dehydration requiring intravenous infusion, sepsis, hypoglycemia and jaundice requiring phototherapy (2).

Cerebral Magnetic Resonance Imaging (MRI) studies have documented morphological maturational processes such as myelination, cortical folding and progressive involution of germinal matrix (3,4), together with changes in specific functions like visual performances (5,6). There is not another gestational age so arbitrary gathered as there is not a specific landmark of an achieved maturation but only an amalgam of disappearing processes (i.e., involution of the germinal matrix) and maturing one (i.e., myelination) (3,4). One of most characteristic developmental neurological process of this period is perhaps the ultimate maturation
Late preterm babies and the risk of neurological damage

of “subplate neurons” making neuronal connections although cannot be associated to any specific brain lesion in case this process is altered (7).

Cortical volume in the late preterm infant is only 53% of the term volume, with approximately half the volume being attained in the last 6 weeks of gestation. In addition, myelinated white matter is present in minimal quantities in an extremely preterm infant, but increases dramatically as term approaches, with a 5-fold volume increase between 35 and 41 weeks (8). Vulnerability of specific neuronal populations in the late preterm is due to multiple factors but, like white matter vulnerability in the early-preterm brain, excitotoxicity and oxidative stress may play a significant role in late-preterm injury. For example, at that stage there is an over-expression of glutamate receptors in regions like the basal ganglia (9). Those receptors are necessary for long-term potentiation and connectivity, but after an insult, their activity can lead to the production of nitrogen and oxygen free radicals that can injure nearby cells. Basal ganglia and thalami are also recognized as metabolically active zones with increased energy requirements which contribute to their particular vulnerability to acute hypoxic insults.

For these reasons late preterm babies are exposed to a wider spectrum of brain lesions common to both most premature and more mature babies as they can develop not only germinal matrix-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (cPVL) (10) but also arterial/venous stroke (11,12), hypoxic-ischemic encephalopathy (HIE) (13), and those parenchymal injuries following hypoglycaemia. The adding problem is the paucity of the related clinical symptoms compared to more term babies therefore these lesions can remain undiagnosed until later in childhood, and may contribute to explain the increased risk of impaired neurobehavioral outcome reported in the literature.

The wide range of cerebral lesions affecting “late preterm babies”

The peculiar contradiction of the highly unspecific brain vulnerability of babies born between 34 and 36 weeks + 6 days make possible for these babies to develop any kind of known brain lesions including those affecting the most premature babies (i.e., an intraventricular haemorrhage) and lesions affecting more typically term babies like asphyxia and stroke (14). In addition, you can have a variable number of different cerebral lesions affecting the same baby at the same time. A very indicative lesion of this multipotential brain vulnerability is showed in case of venous thrombosis (15). A very late appearance of a mild intraventricular haemorrhage together with periventricular white matter changes is very suspicious for a venous thrombosis of the deep venous system. At 34 wks’GA is still possible to have an intraventricular bleed from the remaining germinal matrix at the caudo-thalami notch and white matter bilateral lesions due to involvement of the medullary veins mimicking a PVL lesions (15,16,17). This process can be triggered by the increased venous pressure occurring during thrombosis of the deep venous system (i.e., internal cerebral vein, vein of galen or straight sinus) (15,16).

Periventricular leukomalacia

Although the incidence of the most severe cystic forms of PVL has dramatically decreased in very low birth weight babies it is our impression that some unexpected and clinically very subtle forms of PVL are still possible in less premature, like the “late preterm babies”. We believe these are those forms potentially linked to chorioamnionitis, a condition very likely to have been over emphasized in the pathogenesis of the almost disappeared PVL (10). Other milder form of PVL, usually referred to as “punctate lesions”, predominantly linearly organized and bordering the lateral ventricles are likely to be present in late preterm babies although good epidemiological studies are lacking in this field (18).

Arterial stroke

In most cases, like for arterial stroke affecting term babies, arterial stroke results from placental emboli passing through the patent foramen ovale into the aorta, where the branching of the left common carotid
offers the easiest anatomical path. The left middle cerebral artery, in fact, is the most commonly involved vessel. Injury usually involves both the white matter and the cortex, with the posterior white matter being involved more frequently than the anterior regions (11,12,19). These injuries also affect the brain of premature babies of gestational age above 32 weeks with a similar pattern of lesions involving major branches of arteries, while involvement of the smaller lenticulostriate branches seems to be more common in preterm infants with GA of 28–32 weeks. It remains difficult to identify a specific pathogenesis for arterial infarctions in the minor arterial branches. These younger babies are most often the ones receiving intensive care, and small air bubbles which might pass through the heart via the foramen ovale after insertion of an umbilical venous catheter have been reported as a potential pathogenetic mechanism (19). However, only twin-to-twin transfusion syndrome, foetal heart rate abnormality and hypoglycaemia have been found to be significant and independent risk factors for developing arterial infarctions in the entire population of preterm babies (20,21). No maternal risk factors have been identified. With regard to neurodevelopmental outcome, infants with a main branch arterial infarction are at greater risk of motor/cognitive impairment compared to those with lenticulostriate branches. Preterm compared to term babies have more language problems at 2 years of post-conceptional age (20,21).

**Asphyxia**

Studies of hypoxic-ischaemic encephalopathy (HIE) in late preterm infants demonstrate that in this category hypoxic insult mainly affects the grey matter, but the sites may differ compared to the more mature term brain. Basal ganglia are most frequently involved, particularly the ventro-lateral thalami and posterior putamen, as occurs in term babies (13). Late preterm infants are more likely to show brainstem lesions compared to term infants, indicating an increased susceptibility of the brain stem at these slightly younger gestational ages. Less frequently, injury may also occur to the hippocampus, the cerebral cortex and the subcortical white matter, particularly the perirolandic region. It is interesting to note that the late preterm infant does not often show cortical abnormalities around the central sulcus, which is, on the contrary, a frequent finding in-term infants. It is likely that this region becomes more vulnerable at term due to its active myelination during the very last weeks of gestation (13). This observation confirms that the metabolic demands of myelination may compound the increased vulnerability of cortical neurons and brainstem, respectively, at more and less mature gestational ages. Ischaemic lesions of the basal ganglia and thalami are associated with cerebral palsy and cognitive impairment. In the case of a severe insult, these lesions can be accompanied by abnormalities in specific cortical regions and in the adjacent subcortical white matter, exacerbating the cognitive deficit. Coexisting abnormal MRI signal intensity in the posterior limb of the internal capsule is a powerful predictor of motor outcome severity (13).

**Cerebral palsy in late preterm and intraterme growth retardation**

Two thirds of cerebral palsy arises in the 97% of singletons born at or after 35 weeks of gestation (22). The current impression is that the prevalence of cerebral palsy in these relatively mature neonates, unlike that of survivors of very preterm birth, has not fallen in recent decades. In very recent and convincing studies in which the contribution of potentially asphyxial birth events, inflammation, fetal growth restriction, and birth defects recognized by age 6 years to each of these outcomes was evaluated it emerged that foetal growth restriction and birth defects recognized by age 6 years were more substantial contributors to cerebral palsy and neonatal death than potentially asphyxial birth events and inflammation (22).

The long-term neurological impairment frequently seen in children who showed intrauterine growth retardation (IUGR) cannot be attributed to the presence of overt brain lesions (23). Conventional MR imaging has failed to show even more subtle lesions in IUGR babies, while the number of DTI studies are booming in the search for a common pattern of developmental abnormality. Whatever sophisticated neurological techniques may be used to study brain development,
Late preterm babies and the risk of neurological damage

the risk of brain damage in IUGR neonates could reflect both the liabilities of intrauterine compromise and, in minor entity, the penalties of prematurity. In addition, the exact pathogenetic meaning of “brain sparing”, which is not always a guarantee of the full protection of brain development during intrauterine life, needs to be better understood, as in our experience this was associated to an impairment of myelination (24).

Conclusion

An exact knowledge of the specific contribution of each risk factor for brain vulnerability of late preterm babies is far from being understood as large studies with epidemiological insights are very difficult to be performed. It is likely that gestational ages at birth with occurrence of neonatal comorbidities are the most important risk factors for detecting brain lesions in late preterm population especially in those born at 34 weeks more than at 36 weeks of gestation (25).

In addition to difficulties in diagnosing minor brain lesions and correlating these to specific minor neurological impairment we should not forget the possibility that “late preterm babies” may present neurological clinical impairments in the absence of recognized morphological lesions even with use of MRI imaging (25). The problem is further compounded by the fact that we are less aware of the pathogenetic mechanisms causing neurological impairments in late preterm babies since we can only postulate the likely areas of vulnerability that would seem to be subcortically located, and that particularly affect the subplate neurons.

Understanding early human brain development is of great clinical importance, as many neurological and neurobehavioral disorders have their origin in early structural and functional cerebral organization and maturation. Technological advances in neonatal brain imaging are progressively giving more insights for the understanding of disorders of neonatal brain. In these population of preterm babies the need for always more sophisticated neuro radiological studies has to be accompanied by improved skills in identifying even those very subtle clinical signs of impairment deserving further investigations. In this way we may hope to better understand why some studies highlight that the risk of developmental delay or disability was 36% higher among late preterm infants compared with term infants (26).

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Correspondance:
Luca Romenghi, MD
Terapia Intensiva Neonatale
Istituto Giannina Gaslini IRCCS
Genova, Italy
E-mail: patologianeonatale@ospedale-gaslini.ge.it