UPGRADE OF THE PERINATAL PROTOCOLS THE IMPACT ON VERY LOW BIRTH PREMATURE BABIES OUTCOME

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Abstract

Introduction: The study has been conducted in the "Filantropia" OG Clinical Hospital, before and after the review of obstetrical protocols for high premature birth risk pregnancies, as well as the protocols for respiratory distress syndrome in premature babies, specific for the neonatology department.

Aim: The impact on morbidity and mortality in very low birth weight (VLBW) premature babies.

Methods: This is a retrospective study comparing premature babies with VG<34 weeks, born between 2012 (n=96) and 2013 (n=150) in Filantropia Maternity. Starting with 2013, the following protocols were updated: perinatal care of pregnancies at risk for preterm birth, resuscitation and stabilizing the premature babies within the delivery room, supportive treatment and standard care of premature babies with SDR. The motivation behind this study was to verify the impact of some modifications made in the clinical protocols. The following parameters were compared: indication and time under mechanical ventilation, surfactant administration, duration of oxygen therapy, types of ventilation support, daily care, rate of complications, length of hospitalization. The information was gathered and processed in the statistics analysis program EpiInfo 2007.

Results: There was a decrease in SDR severity, revealed by the decline in premature babies who required mechanical ventilation (64% in 2012 versus 51% in 2013), and the higher prevalence of non-invasive ventilation in 2013 (26% in 2012 versus 44% in 2013). Also, a decrease of the medium duration of ventilation was noticed (4.2 days versus 6.4 but not statistically significant p value = 0.059) and in oxygen therapy length (8.2 days versus 16.6, p=0.0022), also a decrease in severe brain hemorrhage 20% (n=16) versus 14% (n=19) p value = 0.087.

Conclusions: It is necessary to elaborate, upgrade and always follow the specific protocols for obstetrical and NICU departments in order to improve the neonatal outcome of preterm babies with GA lower than 34 weeks.

Key words: premature birth, premature, mechanical ventilation, oxygen therapy

Introduction

Premature births represent a great challenge for the obstetricians, as well as for the neonatologists. Neonatal respiratory distress syndrome represents one of the most acute pathology for finding the best strategy, in order to ensure survival and to decrease complications. These strategies begin before birth, continue in the delivery room and extend to the neonatal intensive care units.

In the last years, many of the treatment guides for the neonatal respiratory distress syndrome have been revised. A first revision was made in the year 2010[1] for the 2007[2] guide, and a second one was made at the end of 2012[3].

These reviews of the European consensus regarding the management of the neonatal respiratory distress syndrome have been a starting point for the updating of existing internal protocols in our clinic.

In 2013, the following protocols have been revised: antenatal care for premature birth risk pregnancies and premature rupture of membranes (≤34 weeks), stabilizing the premature babies in the delivery room, the early use of CPAP and non-invasive methods of ventilation support.

Furthermore, there have been substantial modifications of the nutritional support, through early enteral nutrition and decreased duration of parenteral nutrition. All these modifications have triggered the interest for a feedback on the impact regarding the evolution of the premature babies nursed in our clinic.

Material and method

The study has compared 243 of premature babies with the gestation age of ≤34 weeks, born in SCOG "Filantropia", between the years 2012-2013. The premature babies were split into two distinctive groups before and after the revised protocol : the ones born in 2012 (born - 93) were included in the P (-) group, and the ones born in 2013 (born = 150) were in the P (+) group.

The data was collected in a database and processed in the EpiInfo 7 statistics analysis.

At the beginning of 2013, modifications were made in the obstetrical protocols and in those operating in the neonatal intensive therapy department.

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Prenatal care protocol was updated to include all pregnancies with premature birth risk with gestation age between 24-34 weeks. During premature rupture of membranes, antibiotherapy will be initiated, and the period for tocolytic therapy will be 48 hours, a necessary time for making a complete corticosteroid course. The protocol for the premature birth risk pregnancies and PPROM is presented in table no. 1. If the spontaneous labor does not begin in 48 hours after the membranes rupture and/or after the corticosteroids cure, the attitude will be cesarian section.

In case of intact membranes, a short tocolytic treatment will be made, in order to allow the complete treatment with corticosteroids. If the delivery does not occur within 7 days after the corticosteroids treatment has finished, another treatment will not be applied.

Regarding the stabilization protocol of preterm babies in the delivery room the following modifications have been introduced, since 2012:

- warm diapers, bonnet, bootees, and plastic bags.
- delaying of umbilical cord clamping between 30 to 60 seconds (40 seconds on average)
- use of the lowest tolerated oxygen concentration by air/oxygen blender (30% on average) - the respiratory stabilization with positive pressure with a T piece (Neopuff) and mask.

Regarding the early treatment post-admission in the NICU department, the following therapies were applied:

- CPAP immediately after birth to all premature babies with high risk of respiratory distress (≤30 weeks) until the evaluation of their clinical status (PEEP ≥ 5 cm H2O)
- Intubation and ventilation for severe forms of respiratory distress and/or NCPAP failure. The synchronous modes of ventilation (SIMV) were preferred, with careful monitoring of the pressure/volume respiratory curves.

For the surfactant administration the recommendations from the European guidelines were usually respected:

- prophylactic in the first 15 minutes in the delivery room for GA < 26 weeks, or babies with GA ≤30 weeks, who require intubation.
- Therapeutical indication remained the same - the severe forms of respiratory distress.

The only change in therapeutic administration of surfactant was the case of RDS on NCPAP, with an oxygen concentration (FiO2)>50% and a pressure (PEEP) > 6-7 cm H2O. Sometimes we applied the INSURE procedure, followed by NCPAP.

For protocols of routine care the important changes were:

- A large amount of fluid would prevent the excessive weight loss.
- For hemodynamic stable newborns, early enteral nutrition in the first 24 hours and quick advancement will lead to a decreased use of central lines.
- Shorter antibiotherapy length (until the central line is removed) - Caffeine for premature apnea
- More restrictive transfusion protocols

Table no. 1 Protocol for pregnancies with high risk of premature birth and PPROM*

Gestation age	**Corticotherapy**	**Antibiotherapy**
24 – 27(+6 days) weeks	- Prenatal Corticotherapy - **Betamethassone - 2 doses of 12 mg at 24 hrs** **Dexamethsone - 4 doses of 8 mg at 12 hrs** - tocolytic** and conservatory expectative attitude (the pregnancy will be prolonged close to 34 weeks)	- antibiotic prophylaxis ab initio
28 – 33(+6 days) weeks	- prenatal corticotherapy - **Betamethassone - 2 doses of 12 mg at 24 hrs** **Dexamethsone - 4 doses of 8 mg at 12 hrs** - tocolytic** and conservatory expectative attitude	- antibiotic prophylaxis ab initio
34 – 36(+6 days) weeks	- Prenatal Corticotherapy is not needed	- intrapartum antibiotic prophylaxis in case of infection risk (eg. maternal infection proved with Streptococus B group)
All premature babies	- vaginal exam will be avoided - the delivery mode shall be decided between the obstetrician/neonatologist/mother - there will be a protective attitude, with an atraumatic labor as much as possible (without Oxiton)	

* PPROM – prolonged premature rupture of membranes

** tocolytic maximum 48 hours - the time necessary to complete the cortico- and antibioprophilaxy treatments

Results

This retrospective study enrolled 243 preterm babies, with gestation age <34 weeks. The data regarding the newborn, pregnancy and delivery are presented in table no. 2. Regarding demographic characteristics of the newborns, there are no significant differences (table no. 2). The average gestation period was 30 weeks for both studied groups (Fig. 1)

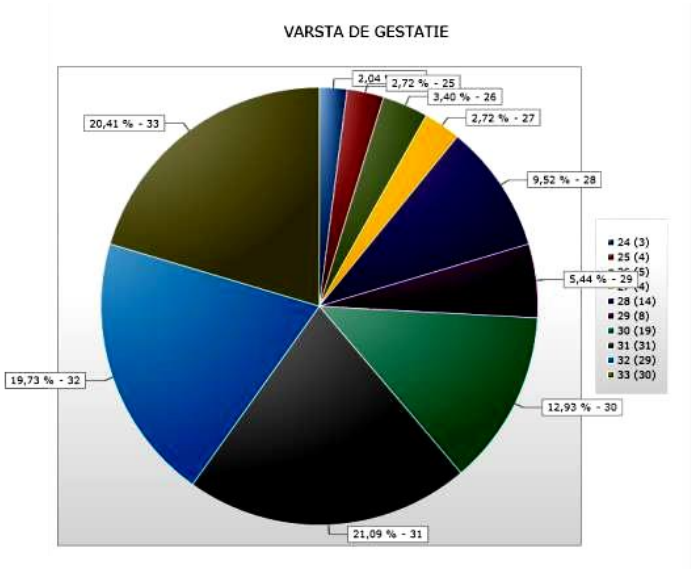

Figure. 1 The repartition according gestation age.

Table no. 2 Pregnancy and birth.

Variables	2012 P (+)	2013 P (-)	P value
No. of prenatal controls (average)	6	7.7	0.64
Corticosteroid prophylaxy	28,38% (23)	52,54% (64)	NS
Hours MR (average)	20.5 +/- 18.5	31.9 +/- 22.9	0.0187
Maternal-fetal infection	16% (14)	27% (38)	0,288021
Way of birth	Caesarian section 51%	65%	0.002
	Spontaneous 49%	35%	

Table no. 3 Demographic characteristics of newborns.

Variables	2012 P (+)	2013 P (-)	P value
Average GA	30.3+/- 2.4	30.4+/-2.2	0.85
Average GN	1501 +/- 459	1496 +/- 446	0.85
Sex M/F	53/47 %	52/48 %	NS

The time between the rupture of membranes and the moment of birth was higher in group P (+), average 31.9 +/- 22.9 hours versus 20.5+/-18.5; this increase is explained by the corticosteroid prophylaxis (p value = 0.0187).

Also, a significant difference can be noticed regarding the way of birth.

In group P (+) the incidence of caesarian section was increased, due to a lack of spontaneous labor in case of PPROM (65% versus 51% p value = 0.002).

In group P (+) the incidence of maternal-fetal infection was higher (16% versus 27%), unrelated to the period of ruptured membranes labor (P-value = 0,90699), possibly due to antibiotics prophylaxis, a standard for all pregnant women with PPROM.

Respiratory distress syndrome was equal in both groups, with less severity in group P(+). In 2013, the percentage of ventilated premature babies was smaller (15% versus 64%) and the non-invasive ventilation mode was predominant (NCPAP used in 44% of the cases with respiratory distress versus 26% in 2012).

The average of ventilation time in group P(+) was 4.2 days versus 6.4 (p value = 0.059), while the length of oxygen therapy was reduced by half: 8.2 days versus 16.6 (p value 0.022) (table no. 4).

By applying the linear regression between more variables (table no. 5), it seems the corticosteroid prophylaxis, the gestation age and the surfactant have significantly influenced the time of oxygen therapy in both groups (Correlation Coefficient: r^2= 0,33). Because no significant differences were observed for gestation age and surfactant administration between the two groups, the prenatal corticosteroids prophylaxis seemed to be the most important variable which influenced the severity of respiratory distress, as well, the time of oxygenotherapy.

The treatment, the evolution and the complications between the 2 groups are presented in the table no. 6.

Table no. 4 Newborns characteristics.

Variables	2012	2013	P value
Apgar score at 5 min	6.6	6.9	0.055
Pulmonary stabilization with Infant T-Piece Resuscitator (Neopuff)	56% (51)	65% (95)	NS
SDR	72% (69)	74% (108)	0.67
VM	64% (58)	51% (75)	0.023
NCPAP	26%(11)	44% (40)	NS
Surfactant	19.5% (18)	21.8% (30)	NS
Average time of mechanical ventilation	6.4	4.2	0.059
Average time of oxygenotherapy	16.6	8.2	0.0022

Table no. 5 Corelation between the ventilation time and other variables (linear regresion).

Variables	Std Error	F-test	P-Value
CORTICOSTEROIDS	1,036	4,1059	0,045396
MATERNAL-FETAL INFECTION	1,093	0,1218	0,727800
GA	0,223	6,2918	0,013738
DISTRESS CAUSE	5,706	0,0211	0,884799
SURFACTANT	1,039	7,5790	0,007014
VENTILATION TYPE (HFOV + SIMV/NCPAP/HFOV)	5,988	0,0576	0,810786
CONSTANT	8,904	6,3036	0,013652

Table no. 6 The outcome of premature babies from the two groups/Current care.

Variables	2012	2013	P value
Caffeine treatment of apnea spells	8,82% (3)	75,51% (37)	0,0130685
PRBC transfusions % Mean	34% (3,8 +/- 2,8650)	25% (1.6+/-0,9554)	0,0019
Nosocomial Infection	13% (12)	5.6% (8)	0.89
HIV Incidence	20% (16)	14% (19)	0.087
ROP Incidence	27% (23)	26% (37)	0.09
Weight at 14 days	1394+/-425	1547+/-420	0.0235

Calories at 14 days cal/kg/day	106 +/-26	112 +/-17	0.8
APT duration	5.2	1.7.	0.001
Start of enteral nutrition	4.2	2.2	0.003
Length of CVC (average)	13,7+/-12,5	8,1+/-3,4	0,000412
Length of hospitalization	37	34	0,505272
Death	14% (13)	7% (10)	NS

The frequency of apnea spells was allmost equal between the two groups 33% (29) versus 35% (29). In 2012, 75% of apnea spells were treated with Aminophylline, unlike 2013 when it was replaced with Caffeine Citrate. Also, caffeine was used in premature babies in NCPAP and, generally, for all premature babies with apnea attacks and gestation age under 30 weeks.

The mean of treatment was 7 days (minimum 1 day - maximum 46 days).

Concerning transfusional therapy in P(+) group there was a significant decrease, 25% versus 34% and the mean of transfusions/child was 1.6+/-0,9 versus 3,8 +/- 2,8 , p value = 0,0019. This can be explained by more restrictive transfusion protocols which combine clinical perception, respiratory therapy, postnatal age and less the "target value" of haemoglobin/haematocrit.

The enteral nutrition was started earlier for group P (+), usually in the second day of life (2.2 versus 4.2 days), with a better caloric input at 14 days (112 +/- 17 cal/kg/day vs. 106 +/- 26 cal/kg/day) and with a better weight gain in the 14th day of life: 1547 +/- 420g vs. 1394 +/- 425g, p value=0.0235. This determined a decrease of total parenteral nutrition (8.1 days versus 13.7 days). The enteral nutrition was made only with fortified maternal milk.

There were no significant differences concerning cerebral hemorrhage (20% versus 14%), but there was a lower proportion of intraventricular hemorrhage of the 3rd and 4th degree in group P(+) (5 children versus 11 children). The average hospitalization time was equal for both groups (35 days) and the death rate was half in the P(+) group 7% versus 14%.

Discussions

There is an European consensus of the guidelines regarding the management of the neonatal respiratory distress syndrome elaborated by a group of experts in neonatology.

They have analyzed the guidelines from 2007 and 2010. In 2013 they made an guideline update based on published studies until the end of 2012.

There are strong evidence for the benefits of corticosteroids prophylaxis in preventing SDR.

The premature birth can be avoided in case of PPROM by using antibiotics and tocolytics for a short period of time, which allows the pregnant woman to be transferred to a perinatal center and to complete the corticosteroids treatment. [4]

Prenatal corticosteroids prophylaxis in women with a high risk of premature delivery, reduces the risk of neonatal death (relative risk 0.55;95 % CI, 0.43-0.72), and by using a single course there are significant less side effects for the mother or the fetus.[5]

Prenatal corticosteroids prophylaxis decreases the risk of intraventricular hemorrhage and NEC[5]. It is recommended in all high risk premature deliveries-under 34 weeks of gestation

Once the corticotherapy is started, the best time for delivery, is between 24 hours and seven days[5]. After 14 days from corticotherapy, steroids benefic input decreases[6] and another course might influence the fetal growth. [7]

Many studies confirm the positive aspect of delayed umbilical cord clamping (30-60 seconds) for premature babies. [8] Almost half of the blood volume of the premature babies can be found in the placenta and by delaying the umbilical cord clamping, the blood volume increases, especially after vaginal delivery. A meta-analysis of 50 studies regarding the delay of umbilical cord clamping in preterms showed that this procedure increases the hematocrit, leads to fewer transfusions, less incidence of NEC and a decrease nearly to 50% of IVH.[9]

The actual protocols suggest the use of a lower oxygen concentration in the delivery room, so that the saturation corresponds to normal values in transitional period. During the transitional period, the saturation measured through pulse-oximetry at the right hand has to gradually increase from 60% to 80% in the first 5 minutes and up to 85% after 10 minutes.[10]

By using early NCPAP with positive pressure control we can stabilize the preterms better after birth, and reduce the need for mechanical ventilation and for surfactant

therapy.[11-12] Infant T-Piece Resuscitator (NeoPuff) measures the inspiratory pressure. The non-invasive respiratory support is defined as any form of ventilation support which is not given through endotracheal tube. Here CPAP, different types of nasal prongs or mask (NIPPV) and oxygen administrated through the high-flow cannulae are included.[13] The sooner it is applied, after birth, the better the chances are to avoid mechanical ventilation and surfactant therapy.

Methylxanthines drugs had been used for a long time in the treatment of prematurity apnea and in order to allow the extubation from mechanical ventilation.

The long term effect of caffeine in apnea of prematurity (CAP) was analyzed in 2006 children with birthweight <1250 g, that received randomized caffeine and a placebo treatment in the first ten days after birth. In children who received caffeine the ventilation was stopped one week before the ones who received the placebo treatment, with a significant decrease of BPD.[14] Monitoring them at 18 months has shown a better evolution for the children treated with caffeine, with lower death rates and neuro-disorders (brain paralysis or slow cognitive).[15]

Regarding routine care in the two groups, several differences regarding fluids and nutritive aportwere noticed. In the delivery rooms, the heating was made by using thermal radiant, warm diapers, bonnets and bootees.

A plastic bag was rarely used for children under 1000g.

In the neonatal intensive care unit, the temperature control was provided by incubators (set temperature 36,5 C, humidity 60 – 70%), in order to decrease the water loss.[16,17]

The fluid aport varied according to the gestational age, weight, and pathology. In the first 24 hours, the fluid volumes varied from 80 – 100 ml/kg in the P (+) group {60 – 80 ml P (-)},with an increase of fluid according to diuresis, weight variations, plasma electrolytes level (especially Na).

There was no increase in the PDA and NEC incidence.[18]

We tried a parenteral nutrition with a protein input ≥ 1 g/kg/day from day one for a faster growth 1g/day until 3,5 g/day. This protein input prevents the negative balance, by increasing the protein synthesis and the nitrogen retention which stimulates the weight growth[19-22].

Carbohydrates ratio in the first 24 hours was 4-5 mg/kg/min, with a daily increase of 1-2 mg/kg/min based on glycemia. We have usually avoided the use of lipids in parenteral nutrition, if the enteral nutrition was initiated in the first 48 hours. The lipids were introduced in the parenteral nutrition if the enteral nutrition was postponed >48 hours, because of cardio-circulatory instability or digestive pathology (NEC). The parenteral nutrition was usually administrated through central lines.

The enteral nutrition was initiated as early as possible (2,2 days on average), and, usually, as soon as there was a cardio-circulatory stability (tisular perfusion and blood pressure at normal values for the age, even with with inotrop support <10 mcg/kg/min).

The start rate was 10 – 20 ml/kg/day using maternal milk, and increasing the rate even in the same day.

The Cochrane studies have shown that there is no NEC risk with an early nutrition and with the fast advancement of it.[23-25].

Conclusions

The protocols for each department are essential, but they have to be in accordance with the recommendations of the european consensus guidelines on the management of neonatal respiratory distress syndrome. Because the latest recommendations are based on clinical studies performed in the last years, the implementing of these protocols greatly improves the outcome of premature babies with respiratory distress syndrome.

References

1. Sweet D, Bevilacqua G, Carnielli V, Greisen G, Plavka R, Saugstad OD, Simeoni U, Speer CP, Valls-I-Soler A, Halliday HL, Working Group on Prematurity of the World Association of Perinatal Medicine, European Association of Perinatal Medicine: European consensus guidelines on the management of neonatal respiratory distress syndrome. J Perinat Med 2007; 35: 175–186.
2. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, Saugstad OD, Simeoni U, Speer CP, Halliday HL, European Association of Perinatal Medicine: European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants – 2010 update. Neonatology 2010; 97: 402–417
3. David G. Sweet Virgilio Carnielli Gorm Greisen Mikko Hallman Eren Ozek Richard Plavka Ola D. Saugstad Umberto Simeoni Christian P. Speer Maximo Vento Henry L. Halliday European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants – 2013 Update Neonatology 2013;103:353–368
4. Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ: Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012; 345:e6226.
5. Roberts D, Dalziel S: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006:CD004454.
6. Gyamfi-Bannerman C, Gilbert S, Landon MB, Spong CY, Rouse DJ, Varner MW, Meis PJ, Wapner RJ, Sorokin Y, Carpenter M, Peaceman AM, O'Sullivan MJ, Sibai BM, Thorp JM, Ramin SM, Mercer BM, Eunice Kennedy Shriver National Institute of Child Health, Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU): Effect of antenatal corticosteroids on respiratory morbidity in singletons after 555–559.
7. Crowther CA, McKinlay CJ, Middleton P, Harding JE: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health

outcomes. Cochrane Database Syst Rev 2011:CD003935.
8. Committee on Obstetric Practice, American College of Obstetricians and Gynecologists: Committee Opinion No. 543. Timing of umbilical cord clamping after birth. Obstet Gynecol 2012; 120: 1522–1526.
9. Rabe H, Diaz-Rossello JL, Duley L, Dowswell T: Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database Syst Rev 2012:CD003248.
10. Finer N, Leone T: Oxygen saturation monitoring for the preterm infant: the evidence basis for current practice. Pediatr Res 2009; 65: 375–380.
11. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, COIN Trial Investigators: Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med 2008; 358: 700–708.
12. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, et al: Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362: 1970–1979.
13. Bancalari E, Claure N: The evidence for noninvasive ventilation.Arch Dis Child Fetal Neonatal Ed 2013; 98:F98–F102.
14. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W, Caffeine for Apnea of Prematurity Trial Group: Caffeine therapy for apnea of prematurity. N Engl J Med 2006; 354: 2112–2121.
15. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, Solimano A, Tin W, Caffeine for Apnea of Prematurity Trial Group: Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007; 357: 1893–1902.
16. Flenady VJ, Woodgate PG: Radiant warmers versus incubators for regulating body temperature in newborn infants. Cochrane Database Syst Rev 2003:CD000435.
17. Sinclair JC: Servo-control for maintaining abdominal skin temperature at 36 ° C in low birth weight infants. Cochrane Database Syst Rev 2002:CD001074.
18. Bell EF, Acarregui MJ: Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2008:CD000503.
19. ParishA, Bhatia J: Early aggressive nutrition for the premature infant. Neonatology 2008; 94: 211–214.
20. Hay WW Jr: Strategies for feeding the preterm infant. Neonatology 2008; 94: 245–254.
21. Ehrenkranz RA: Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol 2007; 31: 48–55.
22. Vlaardingerbroek H, Veldhorst MA, Spronk S, van den Akker CH, van Goudoever JB: Parenteral lipid administration to very-lowbirth- weight infants – early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. Am J Clin Nutr 2012; 96: 255–268.
23. Bombell S, McGuire W: Early trophic feeding for very low birth weight infants. Cochrane Database Syst Rev 2009:CD000504.
24. Morgan J, Young L, McGuire W: Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011:CD001970.
25. Morgan J, Young L, McGuire W: Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2011:CD001241.

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