Mask Versus Nasal Tube for Stabilization of Preterm Infants at Birth: A Randomized Controlled Trial

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objectives: Mask ventilation is associated with airway obstruction and leak. A nasal tube is an alternative interface, but its safety and efficacy have not been tested in extremely preterm infants.

METHODS: An unblinded randomized controlled trial was conducted in Australia, and the Netherlands. Infants were stratified by gestational age (24–25/26–29 weeks) and center. Immediately before birth infants were randomly assigned to receive PPV and/or continuous positive airway pressure with either a nasal tube or a size 00 soft, round silicone mask. Resuscitation protocols were standardized; respiratory support was provided using a T-piece device commencing in room air. Criteria for intubation included need for cardiac compressions, apnea, continuous positive airway pressure >7 cm H2O, and fraction of inspired oxygen >0.4. Primary outcome was endotracheal intubation in the first 24 hours from birth.

RESULTS: Three hundred sixty-three infants were randomly assigned; the study terminated early on the grounds of futility. Baseline variables were similar between groups. Intubation rates in the first 24 hours were 54% and 55% in the nasal tube and face mask groups, respectively (odds ratio: 0.97; 95% confidence interval: 0.63–1.50).

There were no important differences in any of the secondary outcomes within the whole cohort or between the 2 gestational age subgroups.

CONCLUSIONS: In infants at <30 weeks’ gestation receiving PPV in the DR, there were no differences in short-term outcomes using the nasal tube compared with the face mask.

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WHAT’S KNOWN ON THIS SUBJECT: Effective ventilation is fundamental to successful resuscitation of newborns, but face mask leak and airway obstruction are common during manual positive-pressure ventilation in the delivery room, which may compromise resuscitation.

WHAT THIS STUDY ADDS: Compared with a soft, round silicone face mask, using a nasal tube to provide respiratory support in the delivery room does not reduce the rate of intubation but may be a suitable alternative with equivocal efficacy.

abstract

OBJECTIVE: Positive-pressure ventilation (PPV) using a manual ventilation device and a face mask is recommended for compromised newborn infants in the delivery room (DR). Mask ventilation is associated with airway obstruction and leak. A nasal tube is an alternative interface, but its safety and efficacy have not been tested in extremely preterm infants.

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CONCLUSIONS: In infants at <30 weeks’ gestation receiving PPV in the DR, there were no differences in short-term outcomes using the nasal tube compared with the face mask. Pediatrics 2013;132:e381–e388

(Continued on last page)
Neonatal resuscitation is one of the most commonly applied medical interventions, with 5% to 10% of all newly born infants receiving assistance after birth. The mainstay of resuscitation of newly born infants in the delivery room (DR) is the provision of effective assisted inflations. International and national neonatal resuscitation guidelines recommend that a face mask be used with a manual ventilation device to provide initial ventilation after birth. A tight seal between mask and face and appropriate positioning of the infant’s upper airway are important for successful ventilation. However, during the application of manual positive-pressure ventilation (PPV) to infants, leaks around the face mask are common and obstruction of the upper airway may occur, leading to inadequate ventilation. Mask leak and obstruction during mask PPV are often not recognized. They may compromise the delivery of the set positive end-expiratory pressure (PEEP) and appropriate tidal volumes, resulting in delayed establishment of effective gas exchange. Current guidelines for the stabilization of premature infants in the DR recommend the use of an appropriately sized face mask and the provision of PEEP if available.

Most extremely preterm infants cry and breathe immediately after birth and can be successfully stabilized in the DR by using continuous positive airway pressure (CPAP). In the COIN (CPAP or intubation) trial, mask CPAP was initially provided by using a face mask and later replaced with a secure nasal interface to ensure continued CPAP delivery to the infant during transport from the DR to intensive care. Gentle ventilation strategies have been advocated to assist with lung aeration after birth to reduce lung injury and hence short- and long-term morbidity. The use of a nasal interface in the DR has been studied but in more mature infants using long (sustained) inflation times and anatomic face masks as a comparator, and different strategies and manual ventilation devices. A study comparing a nasal interface with a round silicone face mask in the resuscitation of very immature infants, those most at risk of acquired lung injury, has not been performed.

This study aimed to determine whether using a nasal tube to support infants <30 weeks’ gestation at birth was safe and more effective than a round silicone face mask.

METHODS
Patients and Study Design
This 2-center randomized controlled study was conducted between December 2008 and September 2011 at Leiden University Medical Center (LUMC), Netherlands, and the Royal Women’s Hospital (RWH), Melbourne, Australia. Both are tertiary-level perinatal centers with an average of 400 and 650 intensive care admissions per year at LUMC and RWH, respectively. Medical and nursing staff at both participating centers receive training in neonatal resuscitation in accordance with ILCOR recommendations and national resuscitation guidelines. High-risk deliveries are attended by a resuscitation team led by a consultant neonatologist or a neonatal fellow accompanied by neonatal residents and a neonatal nurse. Doctors perform all airway maneuvers and interventions.

If time permitted, consent was obtained before the birth of the child. If this was not possible, consent to use data was sought from the parents as soon as possible after birth. In these cases, a waiver of consent was used to enroll infants and retrospective consent was obtained as per Australian National Health and Medical Research Council guidelines for studies in emergency medicine.

The study was approved by the Human Research and Ethics Committees of LUMC and RWH and was registered in The Netherlands (Dutch Trial Registry, identifier NTR2061) and Australia (Australian and New Zealand Clinical Trials Register, identifier ACTRN 12610000230055).

Randomization
Randomization in blocks of variable sizes was stratified by gestational age (24–25 and 26–29 weeks) and by site. Sequentially numbered, sealed opaque envelopes containing computer-generated treatment groups were maintained in the birthing suite and in operating rooms. Envelopes were opened before birth, allowing time to prepare the nasal tube interface. Although infants were randomly allocated to treatment before birth, they were only enrolled into the study using the allocated interface if they were judged clinically to need intermittent PPV or CPAP. Caregivers were not masked to the intervention.

Study Intervention
Ventilation was provided by a Neopuff Infant Resuscitator T-piece (Fisher & Paykel, Auckland, New Zealand). The flow rate was set at 8 to 10 L/min, and the initial gas was 21% oxygen. The endotracheal tube (ETT) was removed from its packaging and an oblique cut made at the 7-cm marking. The ETT adaptor was then removed and reattached to the distal cut end of the ETT (Fig 3). When randomly assigned to the nasal tube, gentle suctioning of the nares was performed before placement of the interface, which was slid gently down into the nostril to a depth of 3.0 to 4.0 cm either directly or by using a 5F suction catheter over which the nasal tube was railroaded to minimize soft tissue and bony injury during the passage of the tube. To minimize leak, the contralateral nostril was occluded with a finger and the infant’s mouth closed by applying jaw thrust. If the infant was randomly assigned to the face mask, a size 00 Laerdal (Laerdal Medical, Stavanger, Norway)
soft silicone (Fig 3) round mask was applied by using the 2-point top-hold technique.7

If the infant had poor respiratory effort and/or a heart rate (HR) < 100 beats per minute, the team commenced PPV and/or PEEP/CPAP using the allocated interface. If the infant had no or minimal respiratory effort, an initial sustained inflation (SI) was provided (LUMC: 10 seconds SI; RWH: 3 inflations each of 5 seconds duration). If the indication to provide respiratory support was increased work of breathing in a spontaneously breathing infant, in Leiden CPAP/PEEP was provided after SI; in Melbourne, CPAP/PEEP was provided alone. The initial settings on the T-piece ventilator were 30 cm H2O peak inflating pressure and 5 cm H2O PEEP. PPV was provided at 40 to 60 inflations per minute. The range of PEEP/CPAP permitted to stabilize infants in the DR was 5 to 8 cm H2O.

For the primary outcome, infants were intubated in the DR if they met at least one of the following criteria: (1) infant remained apneic and bradycardic (HR < 100 beats per minute) despite 60 seconds of effective PPV, (2) the respiratory effort was poor and HR was < 120 beats per minute after 5 minutes from birth, (3) there was a need for external cardiac compressions, or (4) infant qualified for exogenous surfactant (pulse oxygen saturation [SpO2] < 85% with infant receiving CPAP 8 cm H2O and FiO2 [fraction of inspired oxygen] > 0.4). All infants stabilized with CPAP in the DR were transferred to the NICU with a nasal tube, which was changed to short binasal prongs on arrival. The indications for endotracheal intubation in the first 24 hours within the NICU included at least one of the following: (1) inability to maintain SpO2 in the target range (88%–92%) with a maximum CPAP pressure of 8 cm H2O and FiO2 > 0.4, (2) >1 apnea per hour for 6 hours despite caffeine treatment or any apnea requiring PPV, or (3) a respiratory acidosis (pH < 7.25 and pCO2 > 60 mm Hg and rising) on 2 separate blood gases.

**Primary and Secondary Outcomes**

The primary outcome was intubation in the first 24 hours from birth. Secondary outcomes were Apgar scores, SpO2 in the DR, intubation in the DR, rates of pulmonary air leak syndromes, severe (grade 3 or 4) intraventricular hemorrhage,23 duration of endotracheal ventilation, incidence of bronchopulmonary dysplasia (BPD) and mortality. BPD was defined as infants receiving supplemental oxygen and/or respiratory support at 36 weeks corrected for gestational age. Data were analyzed by intention-to-treat. Prespecified subgroup analyses investigated the effects of gestation and birth weight.

**Sample Size and Statistical Analysis**

We hypothesized that ventilation using the nasal tube would assist in the formation of the infant’s functional residual capacity and facilitate transition more effectively. This method would in turn reduce the risk of early intubation and subsequent lung injury. On the basis of local databases and a higher anticipated incidence of early intubation by using a waiver of consent compared with the COIN trial, we estimated an intubation rate of 55% in the first 24 hours from birth for infants born between 24 and 29 weeks’ gestation. A sample size of 648 (324 in each group) would be sufficient to detect a relative reduction of 20% in the rates of intubation from 55% to 44%, with 80% power and a 2-tailed α error of .05. An independent external data safety monitoring committee reviewed blinded data after 150 and 300 infants were enrolled.

Data were analyzed with Stata software (Intercooled 12; StataCorp, College Station, TX). The data are presented as means (SD) for normally distributed continuous variables and as medians (interquartile range [IQR]) when the distribution was skewed. The clinical characteristics and outcome variables were analyzed by using Student’s t test for parametric and Mann-Whitney U test for nonparametric comparisons of continuous variables, and χ2 test for categorical variables. P values were 2-sided, and P values < .05 were considered statistically significant.

**RESULTS**

A total of 630 (178 at LUMC and 452 at RWH) eligible infants were born at participating centers during the study period (Fig 1). The trial was terminated early on the grounds of futility after a recommendation from our data monitoring committee. There were 20 infants excluded postrandomization, 12 of whom did not receive respiratory support in the DR (6 in each group), and an additional 8 infants were excluded postrandomization because informed consent using the waiver was not obtained (3 randomly assigned to face mask and 5 to nasal tube). Families were not approached if the treating pediatrician deemed this to be inappropriate when dealing with the bereaved families. Thus, 363 infants stabilized in the DR who were randomly assigned to a mask (n = 185) or a nasal tube (n = 178) were included in the final analysis.

The demographic characteristics of the enrolled infants were similar in both groups (Table 1). The demographic characteristics of the 247 eligible infants not randomly assigned were comparable to study participants: 49% male, mean (SD) gestational age of 27.4 (1.7) weeks, mean (SD) birth weight of 1027 (300) g. The primary outcome (Table 2) of endotracheal intubation in the first 24 hours from birth was 54% and 55% in the nasal tube and face mask groups, respectively (odds ratio [OR]: 0.97; 95% confidence interval [CI]: 0.63–1.50). A
total of 199 infants were intubated: 99 in the DR and the remainder in the NICU. The indications for intubation in the DR are shown in Table 3. There were no differences seen between the groups on the indications for intubation in the DR. There were no differences seen in secondary hospital-based outcomes (Table 4), including the composite outcome of either death or BPD at 36 weeks’ corrected gestational age: 36% and 37% in the nasal tube and face mask groups, respectively (OR: 0.97; 95% CI: 0.61–1.51). The median (IQR) days of supplemental oxygen received by infants was 22 (3–60) and 23 (3–54) in the nasal tube and face mask groups, respectively (P = .86). Similarly, there were no differences seen in the total duration of respiratory support (mechanical ventilation plus nasal CPAP): median (IQR) days of 16 (5–41) and 14 (6–42) in the nasal tube and face mask groups, respectively (P = .83).

Table 5 shows the DR interventions by group. There were no differences in the number of infants receiving respiratory support by CPAP alone or a combination of CPAP and PPV. There were no differences seen in the number of infants receiving external cardiac compressions between the groups. Intubation rates (Table 2) were lower in the nasal tube group but did not reach statistical significance (23% vs 31%; OR: 0.65; 95% CI: 0.40–1.07).

There were no important differences seen in the primary or any of the secondary outcomes in subgroup analyses using predefined gestational age and birth weight strata (Tables 6 and 7). There were no episodes of nasal trauma. The nasal tube fell out in 5 infants and required replacement. In 4 infants, the resuscitating team could not pass a size 2.5-mm internal diameter nasal tube in either nares, and these infants received
PPV with a face mask. Their data were analyzed according to allocated interface. There were no significant differences in the pulse oximetry data between the 2 groups in the DR (Fig 2). The median (IQR) HR and SpO2 by group were 142 (120–151) and 140 (123–154) beats per minute \((P = .9)\) and 68% (49–83%) and 65% (46–85%) \((P = .9)\) for the nasal tube and face mask groups, respectively. There were no differences in mortality rates (Table 3).

**Early Cessation of Trial**

Our external data safety committee reviewed masked data at intervals of 150 randomizations. In July 2011, the investigating team discussed the progress of the trial and the merits of continuing. These discussions took place in the light of our inability to recruit more centers to participate in the Netherlands and Australia/New Zealand. The trial statistician (S.M.D.) reviewed the interim data when half of the planned sample size were recruited and suggested that the likelihood of finding a difference between the 2 treatments, if recruitment was completed as planned, was small. The external data safety monitoring committee evaluated the blinded data; they concurred with the trial statistician, and the trial stopped recruiting on the grounds of futility\(^{24}\) in April 2012.

**DISCUSSION**

To our knowledge, this is the first randomized study to compare the use of a nasal interface with a soft, round silicone face mask to provide respiratory support with a T-piece manual ventilation device to infants born between 24 and 29 weeks’ gestation in the DR. The use of a nasal interface did not reduce the rate of intubation, duration of ventilator support, or composite outcome of either death or BPD. Results were consistent across subgroups based on gestational age and birth weight. In addition, there were no serious side effects attributable to the nasal tube. Our findings suggest that both nasal tubes and face mask as shown in Figure 3 are appropriate interfaces to stabilize preterm infants in the DR.

Although International Liaison Committee on Resuscitation (ILCOR) guidelines recommend using a mask,\(^{25}\) our study revealed that a nasal tube may be a suitable alternative to provide respiratory support to preterm infants at birth. Thus, in keeping with ILCOR recommendations,\(^{2}\) personal preference and local expertise may be used to determine an individual unit’s practice. It is difficult to compare our results with previous trials comparing mask and nasal tube in the DR because different methods were used. In contrast to our findings, Capasso et al\(^{19}\) observed a reduction in need for intubation and cardiac massage in the DR when Argyle™ (Covidien, Mansfield, MA) nasal prongs were used compared with a Rendell Baker anatomical face mask (P3 Medical, Bristol, UK). It should be noted that these infants were more mature, the investigators used an anatomical face mask that is no longer available, and the rates of external cardiac compressions were unusually low.

### TABLE 2 Primary Outcome

<table>
<thead>
<tr>
<th>Nasal Tube ((n = 178))</th>
<th>Face Mask ((n = 185))</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal intubation in the first 24 hours</td>
<td>97 (54)</td>
<td>102 (55)</td>
</tr>
<tr>
<td>DR intubation</td>
<td>41 (23)</td>
<td>58 (31)</td>
</tr>
<tr>
<td>NICU intubation</td>
<td>56 (31)</td>
<td>44 (24)</td>
</tr>
</tbody>
</table>

Data are presented as \(n (%)\) and OR (95% CI).

### TABLE 3 Indications for Intubation in the Delivery Room

<table>
<thead>
<tr>
<th>Nasal Tube ((n = 41))</th>
<th>Face Mask ((n = 58))</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea/ poor respiratory effort and bradycardia</td>
<td>23 (56)</td>
<td>32 (55)</td>
</tr>
<tr>
<td>CPAP of 8 cm H(_2)O + FiO(_2) &gt;0.4 to maintain SpO(_2) &gt;85%</td>
<td>15 (37)</td>
<td>23 (40)</td>
</tr>
<tr>
<td>ECC</td>
<td>3 (2)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Data are presented as \(n (%)\) and OR (95% CI). ECC, external cardiac compressions; FiO\(_2\), fraction of inspired oxygen.

### TABLE 4 Secondary Outcomes

<table>
<thead>
<tr>
<th>Nasal Tube ((n = 178))</th>
<th>Face Mask ((n = 185))</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air leak</td>
<td>11 (6)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Postnatal corticosteroids</td>
<td>24 (13)</td>
<td>31 (16)</td>
</tr>
<tr>
<td>BPD</td>
<td>50 (30)</td>
<td>51 (30)</td>
</tr>
<tr>
<td>Death</td>
<td>14 (8)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>Death or BPD</td>
<td>64 (36)</td>
<td>68 (37)</td>
</tr>
<tr>
<td>IVH grade 3/4</td>
<td>13 (7)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>NEC stage 2 or greater</td>
<td>5 (3)</td>
<td>6 (3)</td>
</tr>
</tbody>
</table>

Data are presented as \(n (%)\) and OR (95% CI). IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis.

### TABLE 5 Delivery Room Interventions

<table>
<thead>
<tr>
<th>Nasal Tube ((n = 178))</th>
<th>Face Mask ((n = 185))</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP only</td>
<td>40 (22)</td>
<td>33 (18)</td>
</tr>
<tr>
<td>PPV ± PEEP/CPAP</td>
<td>97 (55)</td>
<td>94 (51)</td>
</tr>
<tr>
<td>Intubation</td>
<td>58 (21)</td>
<td>55 (30)</td>
</tr>
<tr>
<td>ECC (+ intubation)</td>
<td>3 (2)</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

Data are presented as \(n (%)\) and OR (95% CI). ECC, external cardiac compressions.
high in the control group. In our previous trial comparing 2 DR strategies, the interface (nasal tube versus mask) was only one of several differences (T-piece, self-inflating bag, and 1 group receiving an SI) between the 2 strategies. Our current findings suggest that use of a nasal tube may have contributed but was not the most important factor that led to the observed decrease in intubations, mechanical ventilation, and BPD in that study. The other interventions, delivering initial SI and the use of PEEP combined with the undetermined effect of operator and experience in applying DR interventions, are likely to have a synergistic effect with the interface. The use of SI needs additional evaluation.

It is very difficult to create a good seal between the mask and face of the patient, and leak around the mask frequently occurs. Sometimes, to prevent mask leak, caregivers press too firmly, which can cause obstruction. With the use of a nasal tube, although compressive forces are not involved, leak may occur from the contralateral nostril or as a result of an open mouth and inadequate jaw thrust.

### TABLE 6 Subgroup Analysis: Gestational Age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>24–25 Weeks’ Gestation (N = 63)</th>
<th>26–29 Weeks’ Gestation (N = 300)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nasal Tube (n = 30)</td>
<td>Face Mask (n = 33)</td>
</tr>
<tr>
<td>Intubation in the first 24 hours</td>
<td>27 (80)</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Death or BPD at 36 weeks</td>
<td>21 (70)</td>
<td>24 (73)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) and OR (95% CI).

### TABLE 7 Subgroup Analysis: Birth Weight

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Birth Weight &lt;1000 g (N = 194)</th>
<th>Birth Weight ≥1000 g (N = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nasal Tube (n = 101)</td>
<td>Face Mask (n = 93)</td>
</tr>
<tr>
<td>Intubation in the first 24 hours</td>
<td>64 (63)</td>
<td>61 (66)</td>
</tr>
<tr>
<td>Death or BPD at 36 weeks</td>
<td>50 (50)</td>
<td>56 (60)</td>
</tr>
</tbody>
</table>

### FIGURE 2
A, Heart rate at 5 minutes after birth. B, Preductal oxygen saturations (SpO₂) at 5 minutes after birth. Box plots equal median, interquartile range, and range. bpm, beats per minute.

### FIGURE 3
A, A size 00 soft, round silicone mask with 2-point top hold as used in the study. B, a nasal tube (cut from a 2.5-mm internal diameter endotracheal tube); the recommended depth of tube is shown.
which may also cause obstruction. We speculate that the lack of difference in primary outcome may be due to leak and obstruction during both mask and nasal tube ventilation. There were some notable technical issues observed with the use of the nasal tube: in 4 infants, the insertion had to be abandoned because of technical difficulties and these infants received respiratory support with a face mask; in 5 other cases the tube became dislodged during PPV. Lindner et al\textsuperscript{16,20} used a slightly longer nasopharyngeal tube (4–5 cm in length compared with 3–4 cm in our study), which may explain the number of dislodged tubes. Although the population of infants in these studies was similar, a major difference was how PPV was provided: our infants received manual ventilation with a T-piece, whereas in the studies of Lindner et al, PPV was provided by using a time-cycled pressure-limited ventilator. Our study design is a strength, because T-piece ventilators are widely used in DRs around the world.\textsuperscript{27} Our experience with using the nasal tube at this shorter depth was based on the observations of effective delivery of nasal CPAP in the COIN trial.\textsuperscript{13} Our results suggest that the nasal tube may be considered a suitable alternative to the soft, round silicone face mask. The face mask has the advantages of familiarity in clinical practice and as part of training programs and faster application in the DR. We only used a single manufacturer’s mask and a single size and did not analyze our results by experience of the operator. A factor that might have contributed to the lack of difference between devices is that most preterm infants breathe at birth.\textsuperscript{12,28} The interaction between spontaneous breaths and manual inflations has been shown to play an important role in creating and maintaining functional residual capacity at birth.\textsuperscript{28,29} An infant’s spontaneous efforts may minimize the effect of inefficient ventilation provided by the clinician. We anticipated recruiting more centers to reach the sample size within the planned trial period, but unfortunately we were unsuccessful in enlisting the help of other units. Stopping pediatric trials on the grounds of futility should be made once scientific, ethical, and financial considerations have been taken into account. Stopping trials early for these grounds is now under critical review.\textsuperscript{24,30} Caregivers were not blinded to treatment allocation, which can lead to bias in the management of patients, but blinding is difficult to achieve in this type of study. Although we saw a difference in the rates of intubation in the DR, there was no overall difference at 24 hours. Having agreed objective criteria for the stabilization of the infants, including intubation, minimizes this risk, and we saw no protocol violations during the course of the study. With many confounding variables after stabilization in the DR, intubation in the first 24 hours after birth as a primary outcome for DR trials may not be appropriate.

We have shown that DR intervention studies can be implemented using a waiver of consent with the support of families and the medical, nursing, and midwifery teams. It is important to continue to perform large randomized controlled trials with a number of participating centers if we are to increase the evidence base for one of the commonest medical interventions performed annually worldwide.

CONCLUSIONS

The use of a nasal tube to provide respiratory support in the DR to premature infants born before 30 weeks’ gestational age does not reduce the risk of early intubation compared with a soft, silicone, round face mask. Either interface can be used to stabilize preterm infants.

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Mask Versus Nasal Tube for Stabilization of Preterm Infants at Birth: A Randomized Controlled Trial
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