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Optimizing oxygen therapy for preterm infants at birth: Are we there yet?

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Abstract

Premature infants undergo a complex postnatal adaptation at birth. For last two centuries, oxygen has been integral to respiratory support of preterm infants at birth. Excess oxygen can cause oxidative stress and tissue injury. Preterm infants due to lung immaturity may need oxygen for successful transition at birth. Although, considerable progress has been made in the last 3 decades, optimum oxygen therapy for preterm delivery room resuscitation remains unknown. In this review, we discuss the history and physiology behind oxygen therapy in the delivery room, evaluate current literature, provide practice points and point out knowledge gaps of oxygen therapy in preterm infant at birth.

Introduction:

Oxygen is the most commonly used medicine in the delivery room (DR) for resuscitation of preterm neonates and has been in use for more than two centuries.[1] Although a lot of progress has been made in the last 3 decades, optimal DR oxygen therapy for preterm resuscitation remains unknown. In this review, we will discuss historical, physiological and clinical perspectives of DRoxygen therapy in preterm infants and knowledge gaps.

Historical perspective of DR oxygen therapy for preterm infants: Swing of the Pendulum

Michal Sendivogius, a Polish alchemist, first recognized the existence of oxygen in 1604 and described oxygen as the gas which made all animal life possible.[2] Joseph Priestly, usually credited for the discovery of oxygen, warned about oxygen toxicity, as early as in 1770s. He famously wrote: "though the pure dephlogisticated air (oxygen) might be very useful as a medicine, it might not be so proper for us in the usual healthy state of the body for, as

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a candle burns out much faster in dephlogisticated air than in common air, so we might, as may be said, live out too fast and the animal powers be too soon exhausted in this pure kind of air."[2]

However, clinicians recommended using 100% oxygen for sick premature newborns as it was thought that difficulties with extrauterine transition, periodic breathing and apnea occurred due to insufficient oxygenation. Not until an epidemic of retrolental fibroplasia (now called retinopathy of prematurity) occurred in the late 1940s, did physicians begin to recognize toxicity of pure oxygen in preterms.[2] Equally important to note that in 1950s, when attempts were made to limit oxygen exposure to less than 40% in preterm infants to prevent ROP, mortality and prevalence of cerebral palsy increased.[2] It became clear that oxygenation needed to be measured and attempts had to be made to avoid both hyperoxemia and hypoxia. In 1980s, the use of pulse oximetry became standard in neonatal intensive care unit care of preterm infants.[2]

Unfortunately, the lessons learned from the history of oxygen therapy for preterm infants did not transcribe into DR practice. The majority of clinicians believed that newborns who required resuscitation at birth would have had experienced a period of anaerobic metabolism resulting in lactic acidosis and 100% oxygen is required to reverse this condition, to generate ATPs efficiently and to prevent end organ injury. Also, it was believed that brief exposure of 100% oxygen in the DR was not harmful.

Hence, the International Liaison Committee on Resuscitation (ILCOR) since its inception in 1992 till 2005 recommended the use of 100% oxygen for resuscitation of all newborns having difficulty making the transition at birth.[3–6] During the last 4 decades of the previous century, multiple translation, animal and human studies showed clearly that abrupt exposure to oxygen, even briefly, could be toxic especially when tissues have had restricted oxygen exposure throughout their ontogeny.[2] As the concept of oxygen free radicals, oxidative stress, low antioxidant capacity in preterms and their link with apoptosis and reperfusion injury became more established, ILCOR changed its recommendation in 2005.[6] Since then, these recommendations have undergone multiple changes with a focus on avoidance of excess oxygen exposure in preterm infants based on consensus of science at that time. In 2005, ILCOR expressed concerns about the potential adverse effects of 100% oxygen on breathing physiology, cerebral circulation and tissue damage but did not recommend a specific oxygen strategy due to insufficient evidence.[6]

As more evidence mounted to show feasibility of pulse oximetry and titration of oxygen to reduce the oxygen load in the DR, ILCOR in 2010 recommended that goal of oxygen therapy in the DR is to achieve oxygen saturation (SpO_2) values in the interquartile range of preductal saturations measures in healthy term babies following vaginal birth at sea level.[4] These targets can be achieved by starting resuscitation with blended oxygen or air. In 2015, ILCOR recommended that resuscitation of the preterm infants should be initiated with 21–30% oxygen and recommended against using high concentrations of oxygen (65–100%) for initiating resuscitation.[5] There is a rising concern that initiating resuscitation with room air in preterm infants may result in difficulty with extrauterine adaptation and contribute to adverse outcome based on subgroup analysis of the largest randomized controlled trial

conducted till date.[7] These concerns do not bear out in a meta-analysis including the most recent ILCOR systematic review, which included all the randomized control trials performed to date.[8]

Oxygen therapy in preterm at birth- a physiological perspective:

Oxygen therapy and hypoxia: Tissue hypoxia occurs when the oxygen supply is inadequate to meet the demands of the peripheral tissues.[9] This can arise from the inadequacy of oxygenation (passive diffusion of oxygen from alveolus to the pulmonary capillary), inadequate oxygen delivery (rate of oxygen transport from the lungs to peripheral tissues) and/or relatively high oxygen consumption by tissues.[10] Oxygen delivery depends on oxygen content and cardiac output.[10] Oxygen content on the other hand depends on hemoglobin levels and SpO_2.[10] The goal of oxygen therapy is to achieve normoxia and avoid hyperoxemia (excess oxygen in blood) or hypoxemia (low level of oxygen in the blood).

Fetal oxygen physiology: The intrauterine environment is a low-oxygen environment where highest partial pressure of oxygen in the umbilical vein is close to 30 mm Hg.[11–15] The fetus thrives in this environment and maintains normoxia due to fetal hemoglobin (HbF) which shifts the oxygen dissociation curve to the left and allows for efficient loading and unloading of oxygen, higher Hb level and higher cardiac output compared to adults.[10]

Transition from intrauterine to extrauterine environment: On average, HbF saturation is about 50% during labor.[16–18] Birth is a complex physiologic process where fluid absorption from the alveoli and replacement with air reduces pulmonary vascular resistance.[19,20] At birth, systemic blood pressure also increase. Both result in exponential increase in pulmonary blood flow and improved oxygenation. It takes approximately 10 minutes to achieve SpO_2 close to 90% in spontaneously breathing late preterm infants.[21,22]

Pulmonary vascular resistance at birth in preterm infant and oxygen therapy in the DR: At birth, fluid in the alveoli is replaced with air. Mechanical factors, vasoactive factors, neural reflex and increased oxygenation contribute to increase in pulmonary blood flow by 8 to 10 fold, which is critical for pulmonary gas exchange and preload supply to the left ventricle.[19,20] Due to immature architecture and surfactant deficiency, preterm infants are at higher risk of inadequate increase in pulmonary blood flow and inadequate pulmonary transition.[23] It remains unclear if inadequate pulmonary vascular transition at birth in preterm infant can contribute to respiratory morbidity. Effective ventilation of the lungs with optimal inspired oxygen is the key to mediate pulmonary transition. In a recent study by Chandrasekharan et al, ventilation of preterm lambs at birth with 100% oxygen resulted in significant reduction in pulmonary arterial pressure and an increase in pulmonary blood flow but significant hyperoxemia.[23] Ventilation with 21% oxygen did not significantly reduce pulmonary arterial pressure and any increase in PBF was lower. Starting with 21% oxygen and titrating to meet NRP recommended SpO_2 resulted in a modest decrease in pulmonary arterial pressure and a suboptimal increase in pulmonary blood flow. [23] Studies have shown that even though initial ventilation with 100% oxygen enhance the decrease in PVR at birth, it results in significant hyperoxemia, oxidative stress and impaired pulmonary vasodilation in response to subsequent exposure to nitric oxide. [24,25]

Birth an oxidative challenge and vulnerability of preterm infants: Birth is an oxidative challenge as a transition from intrauterine low-oxygen environment to high oxygen extrauterine environment occurs.[9] Relative oxidative stress remains generally high for the first weeks of life.[26] In energy metabolism, oxygen is an electron acceptor in the respiratory chain and gets reduced to water by accepting 4 electrons. Small part of the oxygen requires four intermediate steps to complete this process.[26] Each step results in production of reactive oxygen species within the mitochondria, including superoxide radical (O2-) and hydroxyl radical (OH-). Both are free radicals and highly toxic to the cell if left unchecked. Fortunately, cells have enzymatic antioxidant defenses such as superoxide dismutase, catalase and hydrogen peroxide and non-enzymatic antioxidatns such as reduced glutathione. Unfortunately, preterm infants do not have sufficient enzymatic or non-enzymatic antioxidant defenses which make them prone to oxidative stress.[26,27] In addition, preterm infants have respiratory insufficiency and relative surfactant deficiency which results in the need for supplemental oxygen. Thus, preterm infants are at very high risk of oxidative stress at birth.

Oxygen therapy for preterm infants at birth- a clinical perspective:

Goldilocks principle of DR oxygen therapy: The goal of oxygen therapy in the DR is to use not too little oxygen, so that hypoxemia can be avoided but also not to use too much oxygen so hyperoxemia and resultant oxygen toxicity can be avoided.[1] Studies show a clear link between excess oxygen exposure, oxidative stress and oxidant injury. In animal experiments, oxygen causes DNA damage in a dose dependent manner.[15,26,28–30] Several animal studies demonstrate that hyperoxemic resuscitation results in worse brain injury.[31–35] Hyperoxemic resuscitation has been linked with lung injury, bronchopulmonary dysplasia[36–40], cardiac damage, renal damage[41] and even childhood cancer[42,43]. In contrast, hypoxemia can result in inadequate oxygen delivery and may result in tissue injury, organ damage and adverse clinical outcomes including increased mortality.[2,7,44] Thus, using just the right amount of oxygen may result in normoxia and tissue oxygen delivery will meet the oxygen demands. Normoxia in the DR remains ill-defined as multiple physiologic processes are ongoing for extrauterine adaptation at birth. In addition, it becomes even more difficult to define as preterm infants have respiratory insufficiency, need for supplemental oxygen and low antioxidant defenses.

Which initial fraction of inspired oxygen (FiO_2) should be used to initiate resuscitation in preterm infants: ILCOR recently published a systematic review of initial FiO_2 in preterm newborns < 35 weeks gestational age (GA) requiring respiratory support at birth.[8] In this meta-analysis, 1007 preterm newborns were included from 10 Randomized control trials and 2 long-term follow-ups of included RCTs.[7,8,39,45–54] In addition, four observational studies were also included.[40,55–57] A summary of the studies is included in tables 1, 2 and 3. None of the studies included initiation of resuscitation with intermediate oxygen concentration of 40–50%. It is clear that nearly all preterm infants ≤ 32 weeks require some oxygen supplementation to meet SpO_2 targets.[8] The meta-analysis found no difference in mortality or other clinical outcome when resuscitation was initiated with low oxygen (21–30%) or with high oxygen (60–100%). Based on this meta-analysis, ILCOR currently suggests starting with a lower oxygen concentration (21–30%) compared

to the higher oxygen concentration (60–100%) for preterm (<35 weeks GA) newborns who receive respiratory support at birth with subsequent titration of oxygen concentration using pulse oximetry (weak recommendation, very low certainty of the evidence).[58] In making this recommendation, ILCOR placed value on avoiding exposure of preterm babies to additional oxygen without any proven benefit. Interestingly, 95% confidence intervals for relative risks of critical outcomes were wide enough to include potential harm as well as potential benefits. Heterogeneity between studies, various oxygen titration practices across studies as well as combining old studies with new studies may have affected the results. The current ILCOR recommendation is based on low quality evidence. Adequately powered studies with long term neurodevelopmental outcome data are urgently needed.[58]

What SpO_2 should be targeted during DR resuscitation of preterm infants: Based on preductal saturations obtained by Mariani and colleagues[22] for healthy term newborns who were born vaginally at sea level and breathing spontaneously, ILCOR recommends approximated interquartile range as target SpO_2 during the first 10 minutes after birth.[5] Dawson and colleagues have also published a large cohort study that included similar SpO_2 reference ranges for preterm infants.[21] It is clear from multiple studies that preterm infants ≤ 32 weeks require supplemental oxygen to achieve this target SpO_2.[8] It is also well established that many preterm infants do not meet these target SpO_2 during first 10 minutes after birth with significant time spent outside the recommended range during neonatal resuscitation.[59] In an individual patient analysis by Oei et al, out of 706 preterm infants only 11% were able to reach ILCOR recommended SpO_2 of 80–85% at 5 minutes after birth.[60] If resuscitation is initiated with 21–30% oxygen, it is more likely that those preterm newborns will not meet recommended goal SpO_2. Same study showed that regardless of initial FiO_2, infants who did not reach SpO_2 of 80% by 5 minutes were at higher risk of developing bradycardia, intraventricular hemorrhage and mortality.[60] It remains unclear if these infants did not reach 80% SpO_2 at 5 minutes due to clinical instability and thus were higher risk of developing these morbidities or they were not given adequate oxygen in the DR.

There remains a large variation (as much as 25%) in recommended SpO_2 targets by various councils and clinical practice guidelines.[61] It is unclear if the ILCOR recommended SpO_2 targets are optimal for preterm resuscitation. They are based solely on expert opinion and no randomized controlled trial has compared different target SpO_2 during preterm resuscitation. Given the respiratory insufficiency, poor antioxidant defenses, preterm neonates may require different SpO_2 targets than healthy term infants.

How to titrate the oxygen in the DR: There is no clear guideline for how fast and how frequently FiO_2 should be titrated. None of the study protocols dictated a titration strategy, but left to the clinician on how to titrate the Fio2 to achieve target SpO_2. Studies have shown that there is a delay between dialed FiO_2 on a blender at the proximal end and desired FiO_2 at the distal end reaching the infant.[62,63] The delay could be as high as 30 seconds and it may depend on the device used to deliver oxygen. Dekker et al showed that titration was attempted before the desired FiO_2 was reached in 50% of titrations. It is unclear that such delay is due to leak or circuit design itself. There are no data to guide which

percentage titration should be attempted during neonatal resuscitation. Titration frequency and percentage of change may impact the achieved SpO_2 and time spent below or above SpO_2 targets. Until further evidence is available, clinicians should use their own judgement in how titration of FiO_2 is done during neonatal resuscitation.

What else can impact oxygenation and oxygen delivery during preterm resuscitation in the DR:

1. Ventilation of preterm infants: Infants at birth have fluid filled lungs. For successful transition, this fluid needs to be replaced with air. This transition is impaired in some infants. These infants present with absent or ineffective breathing, desaturation and/or bradycardia at birth. Effective ventilation is the key to successful neonatal resuscitation. Inadequate ventilation can affect oxygenation and SpO_2 in the DR. Studies have shown that SpO_2 levels are different in non-vigorous preterm infants requiring PPV, those requiring CPAP and spontaneously breathing preterm infants.[64,65]

2. Bradycardia: Heart rate remains the most important vital sign to assess response to ongoing resuscitation and adequacy of ventilation. A low heart rate will result in lower tissue oxygen delivery, resulting in hypoxia. We recently conducted a pulled data analysis of 344 preterm infants < 32 weeks GA enrolled in 8 randomized control trials of low vs high oxygen therapy in the DR (unpublished). This BradyPrem Study showed that 38% of preterm infants < 32 weeks experienced prolonged bradycardia (HR < 100 bpm for > 2 minutes).[66] These infants were more likely to have 5 minute SpO_2 < 80% and were at higher risk of mortality and/or Intraventricular hemorrhage.

3. Delayed cord clamping: Spontaneously breathing term and late preterm infants subjected to delayed cord clamping had higher SpO_2 up to 10 minutes after birth.[67] Although interestingly, in an observational study, preterm infants when subjected to delayed cord clamping had lower cerebral regional oxygen saturation and increased oxygen extraction in the first few minutes after birth.[68]

The role of Near Infrared spectroscopy (NIRS) in the DR: NIRS has been used as an adjunct tool to assess brain oxygenation in multiple studies during the first few minutes after birth.[69] It allows one to measure cerebral regional tissue oxygen saturation non-invasively, continuously and within 1–2 minutes of application of the sensor. When utilizing NIRS, one need to carefully consider multiple factors which can affect StO2 such as SpO_2, hemoglobin, cardiac output, local blood flow, blood volume and oxygen extraction by the tissues. Cerebral regional oxygenation reaches plateau earlier compared to SpO_2 which indicates that preferential oxygen delivery to the brain in the first few minutes after birth. Although there are studies with published reference ranges for StO2 values in preterm infants during the transition and a small RCT which shows that NIRS during preterm resuscitation may decrease cerebral hypoxia, caution should be used as optimal cerebral tissue saturation during transition in preterm remains unknown. [69,70]

Oxygen therapy in preterm infants during CPR: Animal data suggest that there is no difference in return of spontaneous circulation or survival of the animal with air or 100% oxygen especially when asphyxia insult is brief.[5] Animal data also suggest that 100% oxygen use during CPR may cause oxidative injury. There are no human data to inform what oxygen concentration should be used during advanced CPR when chest compressions are needed. ILCOR recommends that supplemental oxygen should be used whenever cardiac compressions are needed.[5] This recommendation is an expert opinion to balance the desire to prevent ongoing hypoxic injury with the desire to prevent subsequent hyperoxic injury.

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Practice points:

- Pulse oximetry and oxygen blenders should be used during resuscitation of preterm infants in the DR
- Goal of oxygen therapy in preterm infants during DR resuscitation is to avoid the two extremes of hypoxia and hyperoxemia. These are yet to be clearly defined.
- Current recommendations for oxygen therapy in preterm infants come from low quality evidence. Urgent research is needed to establish an optimal oxygen therapy for preterm infants in the DR.
- In preterm infants < 35 weeks of GA, resuscitation should be initiated with low-oxygen concentrations (21–30%). Initiating resuscitation with high oxygen concentrations (65–100%) should be avoided.
- In preterm infants, oxygen concentration should be titrated to meet the ILCOR recommended SpO_2 targets.
- Oxygen titration should be attempted every 30 seconds and the goal should be to meet the SpO_2 targets.
- SpO_2 < 80% at 5 minutes should be avoided in preterm infants < 32 weeks GA
- Accurate assessment of the heart rate is vital during resuscitation to monitor appropriate transition at birth and efficiency of resuscitation maneuvers if needed.In bradycardic newborn, focus should be to normalize the heart rate by effective ventilation.

Research directions:

- Generate higher quality evidence adequately powered for neurodevelopmental outcomes
- Study of intermediate oxygen concentrations (40–50%) to initiate resuscitation of preterm infants
- Individualization of oxygen therapy. Does different GA, gender, illness severity require different oxygen strategy for resuscitation?
- Optimal SpO_2 targets during preterm DR resuscitation
- How to titrate oxygen during preterm DR resuscitation
- Use of Near infrared spectroscopy during preterm resuscitation
- Oxygen therapy strategies in resource poor countries

Table 1:

Study summary of Randomized and Quasi-randomized controlled trials of low vs high oxygen for preterm infants at birth

Study	Location	Recruitment time, year	Gestational age, wk	Total patients	Low oxygen arm, %	High oxygen arm, %	Oxygen saturation target	Blinded	Additional details
Lundstrøm et al[43]	Denmark	1991–1992	< 33	70	21	80	N/A	No	-Convenience sample - Did not monitor oxygen saturation. Adjusted inspired oxygen concentration according to HR.
Harling et al[44]	United Kingdom	Not reported	< 31	52	50	100	N/A	No	- Did not monitor oxygen saturation during resuscitation
Wang et al[45]	United States	2005–2007	<32	41	21	100	80–85% at 5 minutes 85–90% after 7 minutes	No	-Inspired oxygen was increased if Spo2 <70% at 3 minutes or <85% at 5 minutes -Inspired oxygen was increased also for bradycardia.
Vento et al[46]	Spain	2005–2007	≤ 28	78	30	90	75% at 5 minutes and 85% at 10 minutes	Yes	-Inspired oxygen titration performed every 60 to 90 seconds.
Rabi et al[47]	Canada	2005–2007	≤ 32	106	21	100	85–92% for moderate and low oxygen group	Yes	-The trial included 3 groups: High (100% static), moderate (100%, but titrated for Spo2) and low (21% and titrated for Spo2) -In Moderate and low group inspired oxygen was adjusted 20% every 15 seconds.
Armanian et al[48]	Iran	2009–2010	29–34	32	30	100	HR>100 and sats > 85	No	-Titration by 10% every 60 to 90 seconds
Kapadia et al[37]	Unites states	2010–2011	< 35	88	21	100	High oxygen arm: 8894% Low oxygen Arm: Titrated based on target SpO2 similar to current ILCOR target SpO2	No	-No delayed cord clamping -Low antenatal steroid rate in study infants
Aguar et al[49]	Spain	2008–2012	≤ 28	60	30	60	88–94%	Yes	Published as conference abstract only
Rook et al[50]	Netherlands	2008–2012	<32	193	30	65	88–94% and HR>100 bpm	Yes	-If clinician wanted to titrate oxygen, a switch would disconnect the study blender and connect patients with regular blender which was set at 21% oxygen by default. Blinded supply of oxygen was given for a median of 5 minutes only to the study infants before switching to default 21% oxygen.
Oei et al[7]	Australia, Malaysia, Qatar	2008–2014	<32	287	21	100	65–95% < 5 minutes, 80–95% ≥ 5 minutes	No	-The trial was terminated after 15% of total target enrollment completed due to difficulty in recruitment as a result of loss of equipoise. -Some centers performed delayed cord clamping. -Showed increased risk of death in infants <

Semin Fetal Neonatal Med. Author manuscript; available in PMC 2022 March 28.

Study	Location	Recruitment time, year	Gestational age, wk	Total patients	Low oxygen arm, %	High oxygen arm, %	Oxygen saturation target	Blinded	Additional details
									28 weeks in a post-hoc and underpowered subgroup analysis.

Table 2:

Study summary of Randomized controlled trials of low vs high oxygen for preterm infants at birth with long term outcome data

Study	Location	Recruitment time, year	Gestational age, wk	Total patients	Low oxygen arm, %	High oxygen arm, %	Oxygen saturation target	Blinded	Additional comments
Boronat et al[51]	Spain, Netherlands	2008–2012	< 32	253	30	60 or 65	88–94%	Yes	-Long term outcome data of 2 randomized trial Aguar et al and Rook et al
Thamrin et al[52]	Australia, Malaysia, Qatar	2008–2014	<32	238	21	100	80–95%	No	-Long term outcome data of To2rPido trial. -To ensure optimum follow-up, several forms of assessments used and thus outcome assessment lack uniformity. -Post-hoc exploratory analysis showed Spo2<80% at 5 minutes associated with increased death or NDI.

Table 3:

Study summary of observational studies of low vs high oxygen for preterm infant at birth

Study	Location	Study period, year	Gestational age, wk	Total patients	Low oxygen arm, %	High oxygen arm, %	Oxygen saturation target	Comments
Dawson et al[53]	Australia	2006–2007	< 30 weeks	125	21	100	70–90% at 5 minutes	-In 21% oxygen group, if Spo2 was ≤ 70% at 5 minutes or bradycardia, back-up100% oxygen was given. -If back-up 100% oxygen was given, for Spo2> 90%, FiO2 was reduced by 10% every 30 seconds.
Rabi et al[54]	Canada	2004–2009	≤ 27 weeks	2326	21	100	Not reported	-Primary comparison between Ox100 group (where 100% oxygen was used and was not titrated) and $Ox_{titrate}$ group (where oxygen was titrated) - $Ox_{titrate}$ group was divided into Ox_{21} and $Ox_{22–100}$ to compare initial oxygen concentrations.
Soraisham et al[55]	Canada	2010–2011	< 29 weeks	1509	21	100	Spo2 targets as per Canadian resuscitation guideline. (Similar to ILCOR Spo2 targets)	-Divided into 3 groups: 21%, intermediate (22%−99%) and 100% -No uniform oxygen titration policy. -Intermediate concentrations of oxygen not recorded
Kapadia et al[38]	Unites states	2009–2012	≤ 28 weeks	199	21	100	In high group: 88–94% In low group: As per Neonatal resuscitation program guidelines	-Single center study -Low antenatal steroid rate in study infants -Immediate cord clamping in all infants