



Is There a “Right” Amount of Oxygen for Preterm Infant Stabilization at Birth?

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The amount of oxygen given to preterm infants within the first few minutes of birth is one of the most contentious issues in modern neonatology. Just two decades ago, pure oxygen (FiO₂ 1.0) was standard of care and oximetry monitoring was not routine. Due to concerns about oxidative stress and injury, clinicians rapidly adopted the practice of using less oxygen for the respiratory support of all infants, regardless of gestational maturity and pulmonary function. There is now evidence that initial starting fractional inspired oxygen may not be the only factor involved in providing optimum oxygenation and that the amount of oxygen given to babies within the first 10 min of life is a crucial factor in determining outcomes, including death and neurodevelopmental injury. In addition, evolving practice, such as non-invasive respiratory support and delayed cord clamping, need to be taken into consideration when considering oxygen delivery to preterm infants. This review will discuss evidence to date and address the major knowledge gaps that need to be answered in this pivotal aspect of neonatal practice.

Keywords: oxygen, preterm infant, resuscitation, outcomes, review

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INTRODUCTION

The optimum amount of oxygen required for the respiratory support of newborn infants is one of the most contentious issues in current neonatal practice. The adverse effects of hypoxia are well-known and for centuries, pure oxygen was used without question (1). As recently as the 1960s, oxygen was considered “only to be good” and clinicians were advised to “use (it) liberally” (2), especially with knowledge that birth-related neurological injury could be related to hypoxia (3). The development of the Apgar Score in the 1950s encouraged oxygen treatment (4), even when Apgar herself showed that there was little relationship between birth oxygenation and later intelligence (5).

However, in the 1990s, the Resair study raised the possibility that room air (FiO₂ 0.21) could be used instead of pure oxygen for newborn resuscitation (1). This study was conducted in India (6) where access to oxygen was limited and birth asphyxia rates were high. This study showed that air could be used as safely as oxygen to initiate the resuscitation of hypoxic full-term infants.

Over the next 15 years, an increasing number of studies (7–13) showed that air resuscitation was possible and that using air considerably reduced oxidative stress and injury to major organs such as the heart and kidneys (9). In 2005, a meta-analysis of >1,300 infants by Tan et al. provided compelling evidence that air resuscitation could decrease the risk of death in hypoxic infants by about 30% when compared to oxygen resuscitation (typical Odds Ratio (OR) 0.69, 95% Confidence Intervals (CI): 0.54–0.88; 14).

Thereafter, expert committee recommendations changed significantly. In 1998, pure oxygen was recommended as a supplement to infant ventilation support at birth (14). In 2006, guidelines suggested for the first time that air could be used for term infant resuscitation if oxygen was not available (15). In 2010, guidelines were once again revised to suggest that FiO_2 be manipulated to target preductal SpO_2 readings derived from healthy, full term infants (16–18). These recommendations have not changed to date (19).

Extremely preterm infants may not be hypoxic but still require respiratory support at birth. Many need supplemental oxygen to prevent hypoxia (20). The respiratory needs of preterm infants were acknowledged by international guidelines, which, over the years, varied from no specific recommendation (15), to “initiation of resuscitation with 30 or 90% oxygen and titration to oxygen saturation” (16), to recommending against use of high supplementary oxygen concentrations (65–100%) and advocating for the use of lower oxygen concentrations (21–30%) for infants below 35 weeks gestation (19).

However, whether lower oxygen strategies are best for preterm infants, considering the risk of pulmonary immaturity, is unknown. This review will therefore present current evidence to date for the use of oxygen in the delivery room respiratory support of preterm infants and discuss strategies to address knowledge gaps around contemporary practice. Specifically, it will delineate the historical context behind the shift in practice from higher to lower oxygen, evidence for short and long-term outcomes with lower oxygen resuscitation strategies and then the integration of evidence with current practice, including for more mature (e.g., >32 weeks gestation) preterm infants.

METHODS

This is an objective review of current literature and includes consideration of human and animal studies as well as clinical practice guidelines (CPGs).

The History of Oxygen in Newborn Infant Resuscitation

For millennia, some newborn infants were acknowledged to need assistance to complete the necessary transition from intra to independent extra-uterine life. Chest expansion was the crucial step in this process and was usually accomplished with mouth to mouth by the accoucher (1). Oxygen was added after its discovery by Scheele and Priestley in the eighteenth century by the French anatomist, Francois Chaussier, who, in 1781, was the first to use oxygen to revive “apparently dead” newborn infants (1). Over the next two centuries, oxygen became an indispensable step in the newborn resuscitation process and was given in a wide variety of ways, including via the trachea, into the umbilical veins and even into the stomach [gastric mucosa was purported to have excellent oxygen absorbing properties (1)].

The role of oxygen for newborn resuscitation was firmly entrenched when hypoxia was linked to neurological injury in the 1940s (20). In 1957, the Apgar score was devised to systematically evaluate newborn resuscitation (4). One of the components of

the Apgar score was “color.” Infants who were entirely “pink” received the maximum score of 2, those with blue extremities (acrocyanosis) received a score of 1 and those who were either white or blue, received a score of 0. Most infants became “pinker” with oxygen therapy, resulting in higher color and total scores. There was no apparent relationship between oxygenation at birth and later intellectual development (5) but despite this, the use of oxygen in the delivery room remained unquestioned for decades.

Evolution of Oxygen Administration in the Delivery Room: When Less Became More

Whether a few minutes of exposure to pure oxygen at birth was safe was initially questioned by animal and bench studies (21). In the hypoxic milieu, high energy compounds such as adenosine triphosphate (ATP) are metabolized into hypoxanthine which in turn, is converted by the enzyme xanthine oxidase into xanthine and uric acid. Oxygen is a precursor for this reaction which produces reactive oxygen species (ROS), such as superoxide dismutase and hydrogen peroxide as by-products. The addition of oxygen, e.g., during resuscitation, increases the production of ROS, which, if unmitigated by anti-oxidant protection, eventually causes cellular damage and death (22).

In 1993, Ramji and his colleagues demonstrated that hypoxic full-term infants could be resuscitated with air instead of oxygen. This study was conducted in India, where access to oxygen was limited and costly. The Resair study randomized 84 asphyxiated babies to resuscitation at birth with either air or oxygen. Six infants in the air arm were given oxygen when they failed to respond (by increasing heart rate) within 90 s of life but was no difference in mortality rates or severity and incidence of encephalopathy between the two arms. An infant in the air arm was excluded because of lack of response to resuscitation efforts and was considered a still birth. The authors concluded that air was as safe as oxygen for hypoxic infant resuscitation (6).

Subsequent RCTs, totalling more than 1,500 infants, were then conducted over the next 15 years to examine this question (6–13). These studies led to a series of meta-analyses, with the latest conducted in 2018 (23–30), all of which concluded that air was unequivocally superior to oxygen in reducing the risk of death from birth asphyxia. The latest, conducted in 2018 by Welsford et al., noted that no new evidence had been acquired since 2007 and that the data from which the recommendations were based were low quality for the very important outcomes of mortality (Risk ratio [RR] = 0.73; 95% confidence interval [CI]: 0.57–0.94) and hypoxic ischemic encephalopathy (HIE, 5 RCTs; $n = 1,315$; RR = 0.89; 95% CI: 0.68–1.18). Furthermore, only one study has published on longer-term, i.e., post hospital discharge, outcomes. Saugstad et al. examined 213 of the 323 eligible infants enrolled in the Resair 2 study and found no difference between the air and oxygen groups in rates of cerebral palsy and neurodevelopmental delay (31).

When Less Becomes a “Bit More:” the Implications of Transitional SpO_2 Data

SpO_2 is peripheral capillary oxygen saturation, the fraction of oxygen saturated hemoglobin relative to total (saturated and

unsaturated) hemoglobin in blood. SpO₂ is measured non-invasively by pulse oximetry, which, though not always identical to arterial oxygen saturations (SaO₂), provides a safe, convenient, and inexpensive way of assessing oxygenation within the clinical environment. Normal adult pulse oximetry values range from 95 to 100% but in newborn infants, observational prospective cohort studies show that pre-ductal SpO₂ in healthy term infants may take up to 14 min to minutes to reach $\geq 90\%$ (17, 18, 32–34) and could be as low as 81% by 5 min in otherwise healthy infants delivered by cesarean section (34).

The implications of SpO₂ targeting on infants with lung pathology are uncertain. None of the studies of HIE infants acquired SpO₂ data in response to air resuscitation. Apgar measured oxygen content in 1,787 cord and heel blood samples from 404 infants between birth and 3 days of age. These infants were heterogenous, ranging from healthy infants to those with respiratory distress ($n = 6$), seizures ($n = 7$), and congenital problems, including “mongolism,” microcephaly and muscular dystrophy. There was no apparent relationship between blood oxygen content and IQ in 275 children that returned for developmental testing up to 4 years of age (5).

Nevertheless, recommendations to titrate FiO₂ in response to SpO₂ were made in 2010 (16), primarily from information derived from preterm infants below 30 weeks gestation. In this cohort, exposure to high (>80%) levels of oxygen at birth leads to rapid increase of SpO₂, above 90%, by a few minutes of age (35, 36). In contrast, using air alone led to rapid decline of SpO₂ (37), necessitating supplemental oxygen in almost all infants by 5 min of age to prevent hypoxia (36, 37) while adjusting FiO₂ by graded increments emulated SpO₂ trajectories of healthy term infants (38, 39).

The Impact of a Few Minutes of Oxygenation on the Preterm Infant: the Important Outcomes

The preterm infant responds very differently to oxidative stress from the term infant. Despite lung protective and maturing therapies such as antenatal steroids (40) and exogenous surfactant (41), the preterm infant is exquisitely sensitive to oxidative stress as antioxidant defenses are not acquired sufficiently from the mother or produced *de-novo* until the 3rd trimester (42). The detrimental effects of chronic exposure to high concentrations of oxygen have been known for decades (43, 44) but the effects of hypoxia are equally serious. In an individual patient meta-analysis of five RCTs conducted between 2005 and 2014, enrolling 4,965 infants below 28 weeks gestation, Askie et al. found that nursing infants in lower SpO₂ target ranges (85–89%) decreased the risk of retinopathy of prematurity (ROP) but increased the risk of death and necrotizing enterocolitis [NEC, (45)]. Nevertheless, the impact of just a few minutes of hyper or hypoxia in the preterm infant at birth is uncertain. The short period after birth is often overshadowed by the many events that occur after the infant is admitted into the NICU and a direct relationship between birth resuscitation and later outcomes is unclear.

Can Preterm Infants Be “Resuscitated” With Less Than Pure Oxygen?

In 1989, Svenningsen et al. described the outcomes of 65 Swedish infants below 900 g (22–31 weeks) gestation born between 1984 and 1986. These infants were resuscitated with standard Swedish policy by ventilation with either “air or 30–40% oxygen by 1–5 min if the infant was not breathing and crying within the first minute after birth.” In this cohort, 52% of the infants survived at 28 days and 48% were alive at 1 year. The ontogeny of this policy is unclear but represents the feasibility of lower oxygen respiratory support in a high risk group of extremely preterm infants (46).

Based on this study, Lundstrom et al. randomly assigned a group of preterm infants (median gestation 29 weeks) in Denmark between 1991 and 1992 to resuscitation at birth with either air (FiO₂ 0.21, $n = 34$) or FiO₂ 0.8 ($n = 38$). This was the first RCT to describe both oxygen blending and SpO₂ targeting in either term or preterm infants. In the air group, FiO₂ was increased by steps of 0.1 steps if the “heart rate failed to normalize” within 1 min of age. FiO₂ in the 0.8 group was not altered. Oximetry was determined in only 12 infants from each group because of equipment availability (35). Infants who were given FiO₂ 0.8 had higher SpO₂ readings (>90% by 3 min) compared to a control group of 12 healthy term infants while infants given air had SpO₂ that approximated those of the term infants, reaching >90% only after 7–8 min of life. No infant died in the delivery room but those who were given FiO₂ 0.8 had significantly lower cerebral blood flow, that was correlated with reduced survival in animal studies (47). No other outcomes, including neurodevelopmental outcomes, were described.

The Evidence for Using Less Oxygen in Preterm Infants

To date, 11 RCTs (35, 37–39, 48–54) and four cohort studies (36, 55–57) have been conducted to determine the association between lower and higher oxygen strategies at delivery and preterm (<32 weeks) infant outcomes (see **Table 1**). All of these studies were conducted over a prolonged period of time (>10 years), with enrolment spanning between 1991 (35) and 2014 (54). As a consequence, the methodologies used by these studies were vastly different, especially for SpO₂ targeting. Studies that recruited after publication of the 2010 guidelines (16) adjusted FiO₂ to target SpO₂ recommended by these guidelines (51–53). Older studies targeted SpO₂ levels that were derived from best available evidence at the time of inception (35, 37–39, 48–50, 54). It is important to note that none of the RCTs were large enough to demonstrate any difference in the major outcomes of death and/or disability. Recruitment for the largest study, the To2rpidio study (54), was curtailed at 15% of the target sample due to loss of equipoise against the 100% oxygen arm.

The cohort studies (36, 55–57), nevertheless, suggest that the skills needed for oxygen blending and SpO₂ titration may improve with time, possibly with better outcomes for the infants. These studies compared outcomes after changes to institutional and national delivery oxygen policies. Dawson et al. (36) compared the outcomes of 106 infants below 30 weeks gestation

TABLE 1 | Randomized controlled trials and cohort studies examining the use of lower and higher oxygen strategies in preterm infants.

	FiO ₂	N	Gestation (weeks)	Death [#]	BPD**	PDA [#]	NEC [#]	ROP**	IVH [#]
RANDOMIZED CONTROLLED TRIALS									
Lundstrøm 1995, Enrolled 1991–1992, Denmark (35)									
Low	0.21	34	29 (25–32)	2 (6)	5/32	4 (12)	2 (6)	1 (3)	2 (6)
High	0.8	35	29 (24–32)	6 (17)	2/29	7 (20)	1 (3)	2 (6)	3 (9)
Harling 2005, Enrolment years not available, FiO₂ not changed during resuscitation, no SpO₂ monitoring, UK (48)									
Low	0.5	26	27 (23–31)	4	9/22	4	2	0	NR
High	1.0	26	28 (24–31)	5	7/22	2	0	0	NR
Wang 2008, Enrolment 2005–2007, California, USA (37)									
Low	0.21	18	28.1 ± 2.2	1 (6)	7 (39)	4 (22)	1 (8)	1 (5)	1 (11)
High	1.0	23	27.6 ± 2.1	1 (4)	3 (13)	7 (38)	1 (9)	0	0
Escrig 2008* Enrolment 2005–2007, death data collected at 28 days, Spain (39)									
Low	0.3	19	26.4 ± 1.9	4 (21)	4 (27)	10 (53)	0	1 (7)	2 (11)
High	0.9	23	26.1 ± 1.5	3 (13)	7 (35)	11 (48)	1 (4)	2 (10)	4 (17)
Vento 2009* Enrolment 2007–2008, death data collected at 28 days, Spain (38)									
Low	0.3	37	26.1 ± 1.5	4 (11)	6 (18)	19 (51)	2 (5)	4 (12)	7 (19)
High	0.9	41	26.3 ± 1.3	3 (7)	13 (47)	27 (66)	1 (2)	6 (16)	5 (12)
Rabi 2011* Enrolment between 2005 and 2007, Canada (41)									
Low	0.21	34	29 (28–30) [^]	1	18/33	NR	NR	NR	NR
High	1.0	38	28 (28, 29) [^]	1	22/37	NR	NR	NR	NR
Armanian 2012, Enrolment 2009–2010, 29–34 weeks, Iran (49)									
Low	0.3	16	32	0	NR	NR	NR	NR	NR
High	1.0	16	30.8	0	NR	NR	NR	NR	NR
Kapadia 2013, Enrolment between 2010 and 2011, USA (51)									
Low	0.21	44	30 ± 3	2 (4)	3 (7)	6 (14)	1 (2)	1 (2)	1 (2)
High	0.3	44	30 ± 3	3 (7)	11 (25)	10 (23)	6 (14)	4 (9)	1 (2)
Aguar 2013* Enrolment between 2010 and 2012, Spain (52)									
Low	0.3	34	27.1 ± 1.6	4 (12)	10 (33)	23 (68)	2 (6)	4 (13)	11 (32)
High	0.6	26	26.7 ± 1.5	7 (27)	6 (32)	15 (58)	1 (4)	1 (5)	8 (31)
Rook 2013* Enrolment between 2008 and 2012, Spain, Netherlands (53)									
Low	0.3	99	28.5 (27.1–30.3) [^]	6 (6)	23 (24)	35 (35)	4 (4)	6 (6)	8 (8)
High	0.65	94	29.2 (26.3–30.4) [^]	10 (11)	14 (17)	28 (30)	3 (3)	5 (5)	10 (11)
Oei 2015 Enrolment between 2009 and 2014, Australia, Malaysia, Qatar (54)									
Low	0.21	144	28 ± 2	14 (10)	34 (24)	36 (25)	5 (4)	4 (3)	2 (1)
High	1.0	143	28 ± 2	6 (4)	40 (28)	41 (29)	1 (1)	8 (6)	6 (4)
COHORT STUDIES									
Dawson Enrolment 2006–2007, Australia (36)									
Low	0.21	105	27 ± 1.6	12 (11)	NR	NR	NR	NR	NR
High	1.0	20	27 ± 1.6	3 (15)	NR	NR	NR	NR	NR
Rabi Enrolment 2004–2009 population based, Canada (55)									
Low	0.21–0.4	1244	26 (25,27) ^{^^}	251 (21)	512 (51)	525 (80)	132 (11)	166 (22)	288 (26)
High	1.0	1082	26 (25,27) ^{^^}	192 (18)	458 (51)	630 (90)	96 (9)	165 (24)	215 (23)
Soraisham Enrolment 2010–2011 Population based, Canada (56)									
Low	0.21	445	26.3 ± 1.4	68	181 (47)	248 (56)	43 (10)	51 (16)	59 (13)
Intermediate	0.22–0.99	483	26.3 ± 1.3	72	179 (43)	259 (54)	45 (9)	36 (12)	50 (10)
High	1.0	581	25.8 ± 1.5	124	258 (55) [^]	365 (63) [^]	52 (9)	77 (19)	88 (15)
Kapadia 2013, 2017 Enrolment 2009–2012, institutional, USA (57)									
Low	0.21	89	26 ± 1	17 (19)	14 (19) [^]	27 (30%)	7 (8%)	4 (4%)	10 (11%)
High	1.0	110	26 ± 1	21 (19)	36 (40)	46 (42%)	7 (6%)	14 (13%)	21 (19%)

Death is defined as death before hospital discharge; NR, not reported; BPD, bronchopulmonary dysplasia—need for oxygen/respiratory support at 36 weeks corrected gestation; PDA, patent ductus arteriosus—need for medical and/or surgical treatment; NEC, necrotising enterocolitis, >Bell stage 3; ROP, retinopathy of prematurity, >grade 2 and/or plus disease; IVH, intraventricular hemorrhage, >grade 2 **percentage calculated for survivors, # percentage calculated for all infants.

[^]Data expressed as mean ± standard deviation, n (%), median (range).

^{^^}Median (interquartile range).

[^]p < 0.05.

who were resuscitated with air after a change to institutional policy in 2006, to 20 historical cohorts that were resuscitated with 100% oxygen. This noted that 92% of air infants required supplemental oxygen by 5 min of age and that oxygen titration resulted in similar SpO₂ course to “normal” term and preterm infants. Kapadia et al. compared the outcomes of 110 infants below 28 weeks gestation that were resuscitated with 100% oxygen titrated to target SpO₂ 85–94% to 89 infants resuscitated with initial 21% oxygen, titrated to meet recommended guideline SpO₂ after a change in institutional policy in 2011. No difference in mortality was noted but low oxygen infants had decreased risk of BPD (aOR 0.4, 95% confidence intervals: 0.2–0.9) and higher motor scores on the Bayley Scales of Infants and Toddler Assessment (57).

In Canada, Rabi et al. noted a higher risk of severe neurological injury or death (aOR 1.36, 95% CI: 1.11–1.66) in preterm infants born between 2004 and 2009 after a change in national resuscitation policy from using 100% oxygen to lower oxygen strategies (55). In a later cohort born between 2010 and 2011, Soraisham et al. (56) showed decreased risk of death and/or disability for infants receiving room air ($n = 445$) or intermediate (22–99%, $n = 483$) oxygen compared to those resuscitated with 100% oxygen ($n = 581$).

Starting FiO₂ for Preterm Infants: the Loss of Equipose for Higher Oxygen Strategies

In a survey of 630 clinicians from 25 countries in 2015, almost all (>80%) would initiate resuscitation for preterm infants below 29 weeks gestation with FiO₂ below 0.4. The most commonly used starting FiO₂ was 0.3–0.4. Almost none would use FiO₂ above 0.6 and only four respondents would use pure oxygen as they were limited by equipment availability (58). The lack of equipose toward the use of high initial FiO₂ is demonstrated by the difficulty in recruitment for the To2rpidio study (54) which compared air to FiO₂ 1.0 for resuscitation of infants below 32 weeks gestation.

The RCTs have examined various levels of initial FiO₂, ranging from FiO₂ 0.21–0.3 for low arms and FiO₂ 0.6–1.0 for high arms. All of these studies titrated FiO₂ to different target SpO₂ levels and none compared oxygen titration to the previous gold standard of care: pure oxygen. Importantly, none have examined the FiO₂ levels used most commonly by clinicians: 0.31–0.4 (58) and there are no studies examining impact of initial FiO₂ on non-asphyxiated infants between 32 and 36 weeks gestation.

Importantly, none of the studies were powered sufficiently to examine either survival alone or survival without neurodevelopmental injury. To amalgamate existing data, three meta-analyses have now been conducted. Lui et al. identified 10 studies that randomized 914 infants to initial with FiO₂ < 0.4 or ≥ 0.4. Subgroup analyses were conducted for different FiO₂ strata (0.21 vs. ≥ 0.4 to < 0.6; 0.21 vs. ≥ 0.6 to 1.0; and ≥ 0.3 to < 0.4 vs. ≥ 0.6 to 1.0 and found no difference in the primary outcomes of death and or disability between lower and higher oxygen strategies (59). Welsford et al. included cohort ($n = 4$) as well as RCTs ($n = 10$), totalling 5,697 patients

≤ 35 weeks gestation and again, found no difference in the risk of short-term mortality ($n = 968$, risk ratio (RR) 0.83, 95% confidence interval (CI) 0.50–1.37), long term mortality and neurodevelopmental outcomes (60). Oei et al. (61) examined individual patient data for infants <29 weeks gestation from 8 studies ($n = 504$, 37–39, 50–54) and again, found no difference in the risk of hospital death, bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage (IVH), or retinopathy of prematurity (ROP). See **Table 2** for a summary of meta-analyses.

SpO₂ Targeting: the Other Part of the Oxygen Question and Can It Be Achieved?

The lack of difference noted with initial FiO₂ may be due to the way in which oxygen is titrated during stabilization. In Oei's meta-analysis, blinded studies, where oxygen was titrated by the research team without clinician input, had lower mortality rates in lower oxygen arms [RR 0.46, 95% CI 0.23–0.92, $p = 0.03$; (61)]. The Canadian population studies (55, 56) noted a change in outcomes between two time periods in infants resuscitated with lower oxygen strategies and the necessary skills to titrate oxygen in response to SpO₂ changes undoubtedly require experience (64). In experienced hands, SpO₂ readings can be obtained even in very small infants by 2 min of age (65) but frequent manipulations may be necessary to achieve target SpO₂ levels. SpO₂ targeting is technically difficult, even within the nursery. Lim et al. analyzed 4,034 h of data from 45 infants in a neonatal intensive care unit (median gestation 30 weeks, IQR 27–32) and found that hyperoxia was directly related to the number of patients managed by the nurse. Infants were within target SpO₂ ranges only 31% of the time (median, IQR 19–39%) and experienced a median of 25 FiO₂ adjustments (range 16–41) each day (66).

Within the delivery room, SpO₂ targeting could even be more technically challenging. In an observational study of 78 infants (median 27 weeks gestation), Goos et al. noted large deviations above [median (IQR)] of 4.4% SpO₂ (1.4–6.5), and below target (8.2% (2.8–16.0) SpO₂ in the delivery room. After the first 10 min, SpO₂ levels were, respectively, above and below the limit for 11% (0–27) and 8% (0–23) of the time (67). In bench tests, Dekker et al. noted that the median (IQR) time required to achieved necessary FiO₂ was 34.2 (21.8–69.1) s. During stabilization of preterm infants (median gestation 29 weeks), almost half (49%) of titrations were adjusted prior to achieving desired FiO₂ levels (68). In a prospective observational study of 27 preterm infants (mean 28 weeks gestation, 962 g birthweight), White et al. found that infants spent almost two-thirds of the first 10 min of life with SpO₂ outside target ranges [below by 28%, within by 35% and above by 37% of the time, (69)].

“Normal” SpO₂ for the Preterm Infant and Its Implications

Uncertainty regarding “normal SpO₂” for a preterm infant requiring stabilization and respiratory support in the delivery room is illustrated by the results of a survey of 45 international CPGs. Of these, 36 had gestation specific recommendations,

TABLE 2 | Summary of meta-analyses for the use of oxygen in the delivery room stabilization of preterm infants.

	Studies <i>n</i>	Infants <i>n</i>	Type	Comparator	Gestation (weeks)	Death-short term	BPD	IVH	NEC	ROP	Disability at 2 years
Oei et al. (61)	8 RCT	504	IPD	FiO ₂ ≤ 0.3 vs. ≥ 0.6	<29	0.99 (0.52–1.91)	0.88 (0.68–1.14)	0.81 (0.52–1.27)	1.61 (0.77–3.36)	0.82 (0.46–1.46)	NR
Lui et al. (59)	10	914	Pooled	FiO ₂ </≥ 0.4	<32	1.05 (0.68–1.63)	0.91 (0.72–1.14)	0.93 (0.51–1.71)	0.98 (0.51–1.87)	0.57 (0.24–1.36)	0.82 (0.49–1.35) 2 studies, <i>n</i> = 208
Oei et al.# (62)	8	706	IPD	SpO ₂ <80% vs. >85%	<29	2.1 (1.1–3.9)^	1.2 (0.8–1.8)	4.7 (2.1–10.2)^	NR	1.6 (0.8–3.1)	NR
Welsford et al. (60)	10 RCT 4 cohorts	5,697**	Pooled	FiO ₂ "lower" vs. "higher"	<35	0.83 (0.50–1.37) <i>N</i> = 968	(0.71–1.40) <i>N</i> = 843	0.96 (0.61–1.51) <i>N</i> = 795	1.34 (0.62–2.84) <i>N</i> = 847	0.73 (0.42–1.27) <i>N</i> = 806	1.14 (0.78–1.67) <i>N</i> = 389
					<28	0.92 (0.43–1.94) <i>N</i> = 467	0.90 (0.64–1.28) <i>N</i> = 467	0.84 (0.50–1.40) <i>N</i> = 441	1.62 (0.66–3.99) <i>N</i> = 441	0.75 (0.43–1.33) <i>N</i> = 441	1.08 (0.58–2.03) 1 study, <i>N</i> = 69
Oei et al.# (63)	3 RCT	543 eligible	IPD	FiO ₂ ≤ 0.3 vs. ≥ 0.6 <i>N</i> = 539	<32	NR	NR	NR	NR	NR	Cognitive score <85: 0.8 (0.4–1.5) Any disability: 1.0 (0.8–1.3)
				SpO ₂ <80% vs. ≥80% <i>N</i> = 473	3 < 32	NR	NR	NR	NR	NR	Cognitive score <85: 0.4 (0.2–0.8)^ Any disability: 0.6 (0.5–0.8)^

IPD, Individual Patient Data; BPD, bronchopulmonary dysplasia; IVH, Intraventricular hemorrhage, grades >3; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; *exact FiO₂ undefined, **outcomes reported for RCTs only, ^*p* < 0.05.

Data expressed as Risk Ratio (95% Confidence Intervals) except for # (Odds Ratio, 95% Confidence Intervals).

five did not provide SpO₂ recommendations and 5-min SpO₂ targets differed by up to 20% (70–90%). The most common recommendation was to adjust FiO₂ to target 5-min SpO₂ of 80–85% (70).

However, the consequences of reaching, not reaching or exceeding recommended SpO₂ levels are unknown, not only for the preterm infants but also for term infants. The existing RCTs were designed to assess initial FiO₂ only rather than specific SpO₂ targets, which varied considerably from study to study. In an individual patient data analysis of 768 infants below 32 weeks gestation randomized to either lower (FiO₂ ≤ 0.3) or higher (FiO₂ ≥ 0.6) initial oxygen at delivery, infants that did not reach a minimum of SpO₂ 80% by 5 min were more likely to have lower heart rates (mean difference –8.37 bpm, 95% CI –15.73 to –1.01), develop severe (grade III/IV) IVH (OR 2.4, 95% CI: 1.01–4.11) and to die. The risk of death increased with time taken to reach a minimum SpO₂ of 80% and infants were less likely to reach SpO₂ 80% by 5 min if respiratory support was initiated with less oxygen [FiO₂ 0.3 vs. 0.6, OR 2.63, 95% CI: 1.21–5.74; (62)].

The relevance of SpO₂ on preterm infant outcomes needs further evaluation. In a recent secondary analysis of 284 infants <32 weeks gestation that were enrolled in several delivery room trials, Katheria et al. showed that infants who did not reach a minimum SpO₂ 80% by 5 min (*n* = 100, mean gestation 27.4 weeks) were more likely to die (16 vs. 4%), develop severe IVH (24 vs. 10%), have lower heart rates, require higher mean airway pressures and were given more oxygen compared to infants with higher SpO₂ (71).

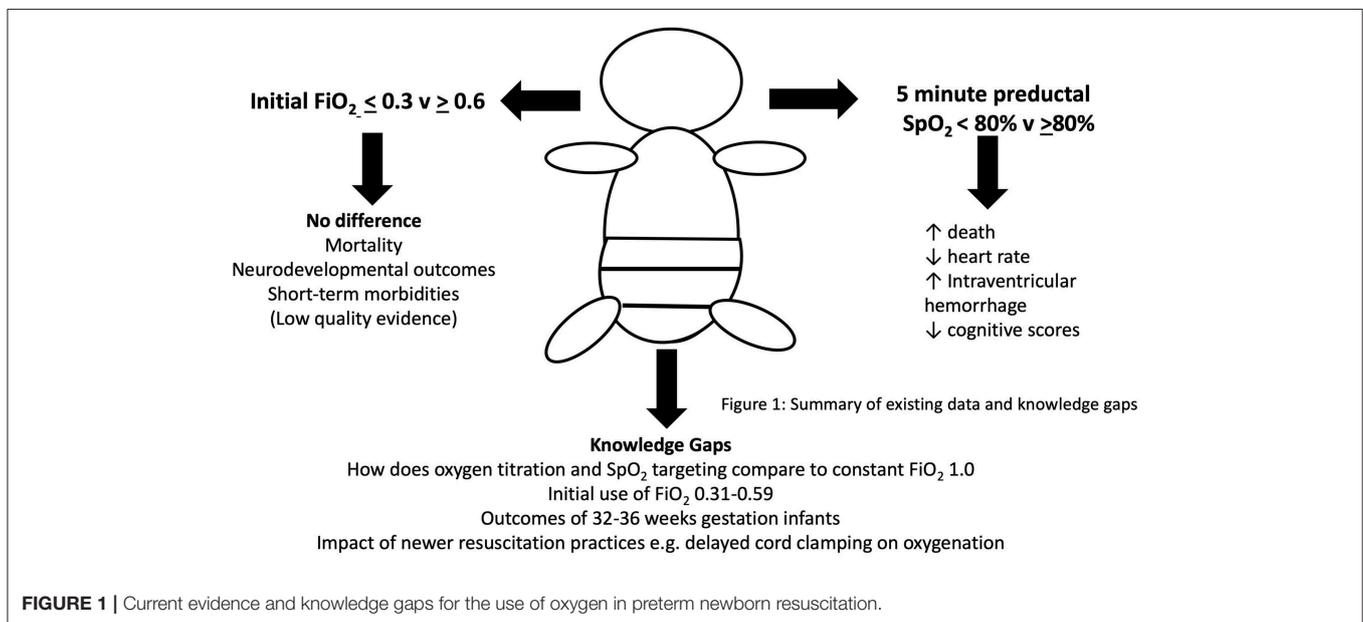
causes rapid cellular injury and compromise. In the early 1990s, Lundstrom et al. noted decreased cerebral blood flow in preterm infants resuscitated with higher initial FiO₂ (0.8) compared to air but as noted before, the implications of this finding were unclear as all infants survived delivery room resuscitation (35). The advent of newer technologies, such as Near Infrared Spectroscopy (NIRS) show that regional cerebral oxygen saturations (rcSO₂) are exquisitely sensitive to changes in FiO₂ even in the first few minutes of life (72). Kenosi et al. measured rcSO₂ in 47 preterm infants (mean gestation 29.4 weeks) who were all initially given FiO₂ 0.3. These infants were then divided into two groups according to their subsequent FiO₂ needs (≤ or ≥0.3). Those needing ≥ FiO₂ 0.3 showed evidence of increased cerebral hypoxia (rsSO₂ < 55%) but no difference in the degree of cerebral hyperoxia, suggesting that infants with SpO₂ may need more rapid upward FiO₂ titration to prevent cerebral hypoxia (73). The COSGOD III study aims to recruit 726 infants <32 weeks gestation to determine if cerebral NIRS measurements can influence the risk of survival and cerebral injury (74). Using rcSO₂ measurements as well as SpO₂ may serve to further inform on optimum oxygen needs for the transitioning preterm infant.

The Association Between SpO₂ at Birth and Cerebral Oxygenation

There is now emerging evidence that longer-term outcomes may be impacted by SpO₂ at birth. Both hypoxia and hyperoxia

The Impact of Oxygenation at Birth and Long-Term Outcomes

No study has compared the current practice of using oxygen titration strategies to the previous standard treatment of using only FiO₂ 1.0. The follow-up cohorts from 2 RCTs: Boronat et al., who examined 206 children below 32 weeks gestation randomized to initial FiO₂ 0.3 or 0.6 (75) and Thamin et al., who examined 238 infants below 32 weeks gestation randomized to resuscitation with either FiO₂ 1.0 or 0.21 (76), found no difference in the major outcomes of



death or disability with different initial FiO_2 . However, meta-analysis of these two studies with individual patient data found significantly lower mean cognitive scores in males ≥ 29 weeks gestation initially given $\text{FiO}_2 \leq 0.3$ compared to those given $\text{FiO}_2 \geq 0.6$. In addition, infants with 5-min $\text{SpO}_2 \geq 80\%$ were significantly less like to be disabled/deceased (OR 0.43, 95% CI: 0.27–0.67) or in survivors, be disabled [OR: 0.57 (0.36–0.89)], compared to those with 5 min $\text{SpO}_2 < 80\%$ (63).

The Way Forward: Individualization May Be the Key

Perhaps the amount of oxygenation needed by preterm infants needs to be individualized. The To_2rpido study, for example, showed that mortality rates of infants ≥ 29 weeks gestation were not influenced by initial FiO_2 , in contrast to infants below 29 weeks who were more likely die if exposed initially to air (54). More mature infants were more likely to overshoot recommended SpO_2 targets despite FiO_2 adjustment if supported was started with higher levels of oxygen (54). The consequences of “overshooting” SpO_2 targets still remain unclear. In the meta-analysis of long-term outcomes of RCTs, mature female infants (≥ 29 weeks gestation) who had respiratory support initiated with higher FiO_2 levels (≥ 0.6) had higher cognitive scores than all other infants, especially male infants > 29 weeks gestation who were given lower initial $\text{FiO}_2 (\leq 0.3)$ (63). Indeed, this could reflect better lung maturity in females. Observations from 102 infants (median gestation 29 weeks) found significantly higher SpO_2 in females in the first 10 min compared to males (77), suggesting that males and very preterm infants may need more oxygen after birth, either by starting on a higher initial FiO_2 or with more rapid oxygen titration strategies.

The Major Knowledge Gaps for Delivery Room Oxygenation of the Preterm Infant

Currently, optimum oxygenation during the first 10 min of life in preterm infants is unknown but data show that oxygen levels, even within the few first minutes, have enormous potential to influence death and longer-term outcomes. However, there are significant deficits to current knowledge that need to be address before contemporary practice can be considered safe (see Figure 1).

For example, research must be conducted to address the needs of more mature preterm infants (32–36 weeks gestation) that are the largest global population of preterm infants ($> 80\%$). This group of infants are at significant risk of neurodevelopmental

issues when compared to full-term infants even though most are considered physically healthy (78). Whether delivery room oxygen strategies have the potential to change their long-term outcomes needs to be determined. Furthermore, the feasibility of oxygen titration strategies in under-resourced countries, which also carry the global burden of prematurity, is unknown. Equipment needed to blend and monitor oxygen use is expensive and clinicians in these countries may be restricted to using either only air or pure oxygen if these are unavailable (79).

Finally, the implications of evolving resuscitation practices on the oxygen needs of the preterm infant need to be evaluated. The clinical trials have so far, not addressed the impact of delivery room practices such as delayed cord clamping (80), less invasive surfactant administration (81), and increasing use of non-invasive respiratory support. Animal and physiological studies of human infants show that these practices may have considerable impact on oxygenation status. For example, glottic opening is enhanced higher (e.g., $\text{FiO}_2 1.0$) oxygen exposure than air, which may then impact on the respiratory status of unintubated infants (82).

CONCLUSIONS AND CLINICAL SUMMARY

In conclusion, current recommendations for the use of oxygen during delivery room stabilization of preterm infants at birth are determined primarily from data that are amalgamated from term infants and older resuscitation strategies. These significant knowledge gaps are acknowledged by expert committees. Even though great importance is placed on initial FiO_2 and the need to avoid hyperoxia, further evaluation of other aspects of oxygen handling, e.g., SpO_2 targeting is needed. Individualization of oxygen strategies also appears necessary, with some infants e.g., males and very preterm infants, requiring more oxygen to prevent hypoxia than females, and older preterm infants. The implications of current recommendations (oxygen targeting) for lower resource countries without access to blending and monitoring equipment, also need to be considered. Further evidence for best practice is needed from large scale, RCTs to determine not only the short-term but also the long-term implications of this practice (83).

AUTHOR CONTRIBUTIONS

JO developed the manuscript and approved the final version for submission. MV revised and approved the final manuscript for submission.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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