CONGENITAL DIAPHRAGMATIC HERNIA

a critical appraisal of perinatal care

Denise Horn-Oudshoorn

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een kritische evaluatie van perinatale zorg

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1 General introduction

Adapted version of:
Perinatal stabilisation of infants born with congenital diaphragmatic hernia: a review of current concepts

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GENERAL INTRODUCTION

The birth defect **congenital diaphragmatic hernia** (CDH) is characterised by incomplete closure of the diaphragm and it affects around 1 in 2500 live born infants, making it a rare disease.[1-3] CDH is associated with significant neonatal morbidity and mortality, with mortality rates around 30% and the majority of deaths occurring in the first year of life.[1,3,4] The diaphragmatic defect can be surgically closed after birth, but survival is determined by the degree of disrupted lung development aggravated by herniation of abdominal organs into the chest during pregnancy.[5,6] The CDH-associated lung disease is characterised by a smaller lung size and by structural and functional changes in the airways and the pulmonary vasculature.[6,7] Structural changes include an increased smooth muscle cell deposition in pulmonary arteries and a reduced total arterial cross-sectional area.[7-10] Pulmonary hypoplasia in infants with CDH results in respiratory insufficiency and cardiovascular dysfunction, with pulmonary hypertension being the main short-term consequence; however, long-term pulmonary sequelae such as bronchopulmonary dysplasia are also often present.[5,6,11,12] The incidence of pulmonary hypertension in the first week of life was reported at almost 70% in a cohort of nearly 3500 infants with CDH.[13] Additionally, the presence of severe pulmonary hypertension at one month of life was associated with a 56% mortality rate before discharge.[14,15] Improving prevention or treatment of CDH-associated lung disease could thus increase the survival rate in infants with CDH.

Recent studies have evaluated **prenatal** interventions that aimed at improving pulmonary development by increasing the gas exchange area and at reducing pulmonary vascular resistance. The benefits of temporary tracheal occlusion, named fetoscopic endoluminal tracheal occlusion (FETO), have been assessed in two randomised clinical trials (*Tracheal occlusion to accelerate lung growth* trials, NCT00763737/ NCT01240057).[16,17] A survival benefit was demonstrated in infants with CDH expected to have severe pulmonary hypoplasia.[17] Pooled analysis of all data also suggested a similar survival benefit in infants expected to have moderate pulmonary hypoplasia when FETO is performed early, meaning between 27 and 30 weeks of gestation.[18] Research has also focussed on prenatal administration of lung development modulating medication such as sildenafil, a phosphodiesterase-5 inhibitor. In preclinical animal CDH models, prenatal administration of sildenafil resulted in improved pulmonary vascular development.[19-21] However, further exploration of its clinical value was hampered after premature cessation of the STRIDER trial (*Sildenafil therapy in dismal prognosis early onset fetal growth restriction*) because of safety concerns.[22] Prenatal administration in cases with severe fetal growth restriction, and thus normal lung development, appeared to be associated with an increased risk of neonatal pulmonary

hypertension.[23] This prompted most Competent Authorities to halt all ongoing clinical studies concerning the prenatal use of sildenafil and studies have not been reapproved yet, despite more nuanced conclusions based on a secondary analysis of the STRIDER data.[24] A recent study in the nitrofen rat CDH model demonstrated that maternally administered treprostinil, a prostacyclin analogue with vasodilating effects, resulted in a significant reduction of muscularisation in the fetal pulmonary arterioles.[25] In combination with earlier studies on the tolerability and effects of treprostinil in infants with CDH, prenatal administration seems promising.[26-28]

Interventions **after birth** mainly focus on decreasing the high pulmonary vascular resistance. Postnatal protocols currently recommend the use of the vasodilator inhaled nitric oxide (iNO) as first choice in pulmonary hypertension treatment although its effect on pulmonary hypertension secondary to CDH is variable and only present in 30% of the cases.[13,29-33] Sildenafil is a commonly used alternative with similar individual variation in efficacy when treating pulmonary hypertension secondary to CDH.[34-36] There is currently still equipoise regarding the first choice of therapy for pulmonary hypertension in CDH. This equipoise was addressed in a randomised controlled trial, but this trial was prematurely terminated because of poor recruitment and its results are anticipated this year.[37] Furthermore, the importance of left ventricular dysfunction in infants with CDH is now recognised, warranting the need for treatment modalities targeting cardiac function, such as milrinone, a phosphodiesterase-3 inhibitor with vasodilating, inotropic, and lusitropic effects.[38-41] As the degree of pulmonary hypertension and cardiac failure is variable in each infant with CDH, individualised management on the intensive care unit is essential.

One aspect of the continuum of care that starts at diagnosis of the diaphragmatic defect and continues until after birth has largely been overlooked in clinical research, being the **fetal-to-neonatal transition** at birth. Although one prospective randomised trial aimed at determining the optimal initial ventilation mode in CDH, no significant differences were found between high-frequency oscillation ventilation and conventional mechanical ventilation.[42] Moreover, studies on respiratory support modalities other than intubation have not been conducted at all, probably due to the current recommendation of immediate intubation. As a result of the scarcity of clinical trials in the delivery room, the current standard of care has not undergone significant changes over the past decades.

Concluding, despite major efforts to improve clinical care for infants with CDH, numerous challenges still exist. This thesis reports a critical appraisal of three important topics in clinical care for infants with CDH: prenatal parental counselling, routine

management during the fetal-to-neonatal transition, and postnatal predictors to enable individualised care.

BEFORE BIRTH

Currently, 70-80% of all CDH cases are detected prior to birth.[43,44] Following the prenatal diagnosis of CDH, parents are confronted with unexpected dilemmas such as whether to perform genetic testing and whether to continue the pregnancy. Results from studies in pregnancies complicated by other genetic or anatomical abnormalities demonstrated that both fetal factors (e.g. disease severity) as well as parental factors (e.g. ethnicity) may affect the parental decision.[45-53] Knowledge of which specific factors are important in the parental decision to terminate the pregnancy in case of a fetal CDH could support medical staff and parents in making a shared decision.

Infants born with CDH have a higher risk of being born preterm than infants without any malformations.[16,17,54-58] Prenatal counselling of parents regarding postnatal outcomes is based on prediction models that have been mainly validated for term born infants, while prematurity-related morbidity could be a confounder for the association between prenatal parameters for severity of CDH and mortality. CDH-related mortality is mainly determined by the severity of pulmonary hypoplasia, which is best estimated by the combination of the observed to expected lung-to-head ratio (o/e LHR), liver position, and side of the defect.[31,59,60] A better understanding of the association between those prenatal parameters and postnatal outcomes in preterm born infants with CDH could aid medical staff in counselling parents facing imminent preterm birth.

AT BIRTH

Delivery room management: current guidelines

For most infants with CDH the major challenges start at birth, the moment a fetus transitions to a neonate. To facilitate this transition, most infants with CDH are stabilised according to routine management that includes immediate cord clamping and respiratory support. However, current guidelines regarding resuscitation of infants with CDH are predominantly opinion-based, since trials assessing delivery room management are lacking. Several large European centres published a consensus document, which was updated in 2015 (CDH EURO Consortium), and a similar guideline by the Canadian CDH Collaborative was published in 2018.[31,61] In contrast, the American Pediatric

Surgical Association guideline does not provide recommendations regarding delivery room management in infants with CDH at all.[62] In both the European and Canadian guidelines, the key principle of stabilisation is to establish adequate perfusion and oxygenation while avoiding high airway pressures.[31,61] Non-invasive respiratory support is avoided because of the potential risk of gastro-intestinal distension. Accordingly, most infants are intubated rapidly after birth. To facilitate respiratory support, the umbilical cord is clamped immediately after birth yet both guidelines do not dictate the exact timing of cord clamping.[31,61] Other than that, clear recommendations on sedation prior to intubation are not provided. A better understanding of the exact cardiorespiratory changes occurring during the fetal-to-neonatal transition in infants with CDH is required to comprehend how current guidelines could be improved.

Fetal-to-neonatal transition

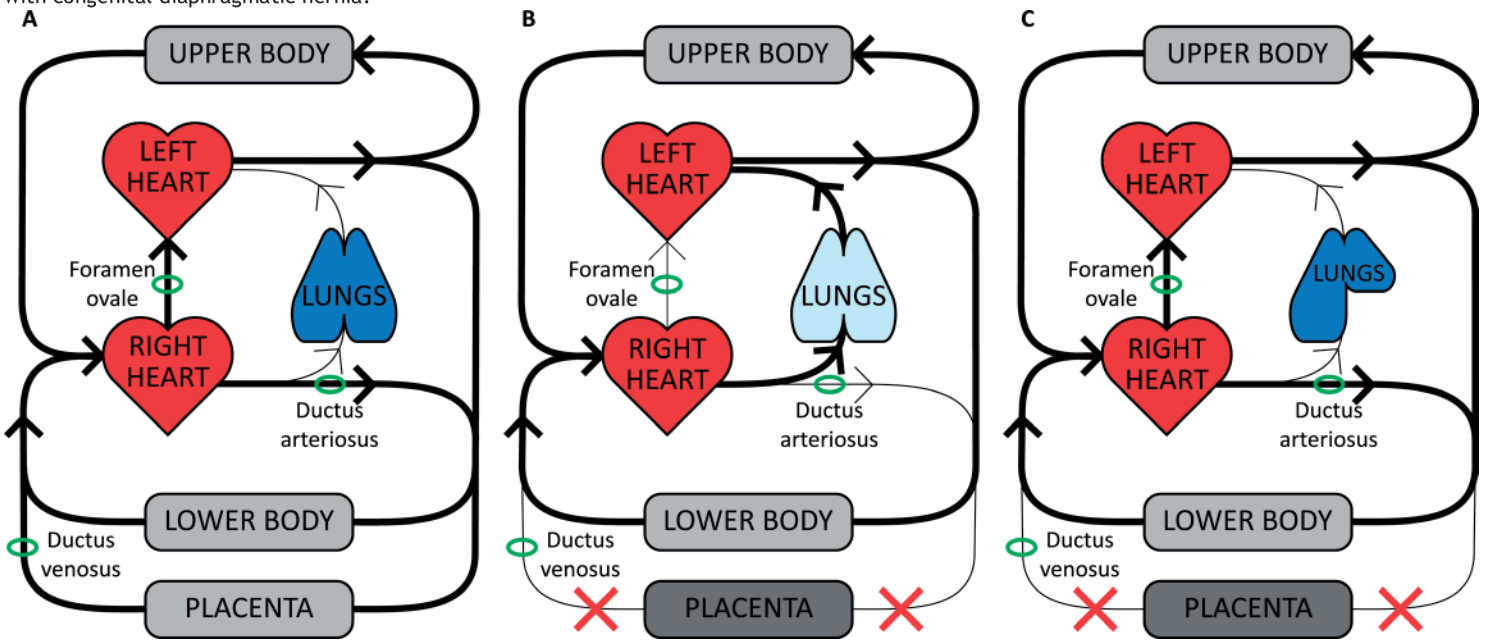
Fetal circulation

In the fetal circulation (Figure 1A), left ventricular (LV) preload is mainly derived from umbilical venous blood flow that is preferentially streamed to the left atrium via the ductus venosus and the right-to-left shunt through the foramen ovale.[63,64] The placental circulation provides oxygenation of fetal blood and greatly reduces overall systemic vascular resistance because placental vascular resistance is low.[63,64] Pulmonary vascular resistance is high since the fetal lungs are not aerated and as a result pulmonary blood flow is low. Thus, the majority of the right ventricular output shunts from right to left through the ductus arteriosus to enter the systemic circulation.[63]

Fetal-to-neonatal transition in healthy infants

At the time of cord clamping several adaptations in the cardiovascular and pulmonary system occur as the low resistance placental vascular bed is removed from the systemic circulation (Figure 1B). The loss of umbilical venous return decreases LV preload by 30-50% and, when combined with an instantaneous increase in systemic vascular resistance, cord clamping results in a decrease in cardiac output as reflected by lower stroke volume and heart rate.[63,64] This likely explains the observed transient bradycardia in the heart rate nomograms of healthy infants.[65,66] Lung aeration triggers the transformation of the fetal circulation into the neonatal phenotype by stimulating a decrease in pulmonary vascular resistance and an increase in pulmonary blood flow, which then re-establishes the preload lost on cord clamping.[63] Lung aeration is established rapidly after birth and when this occurs before clamping the umbilical cord, hypoxia and haemodynamic compromise will be avoided.[6]

Figure 1 Cardiopulmonary physiology. (A) Fetal phenotype. (B) Fetal-to-neonatal transition in healthy infants. (C) Fetal-to-neonatal transition in infants with congenital diaphragmatic hernia.



Fetal-to-neonatal transition in infants with CDH

For almost all infants born with CDH, transitioning to a neonatal phenotype is complicated and medical intervention is essential for survival. However, our knowledge of how pulmonary hypoplasia affects the cardiopulmonary physiological changes during the transition period is largely based on animal models. The hypoplastic lungs of infants with CDH have low compliance, resulting in delayed lung aeration after birth (Figure 1C).[67] In particular, airway liquid clearance will be impeded because of an increased resistance for liquid to flow down through the airways due to their smaller total cross-sectional area, in combination with a reduced surface area for liquid movement into the perialveolar tissue.[7,67] Since lung aeration is the most important trigger for decreasing pulmonary vascular resistance and augmenting pulmonary blood flow, impaired airway liquid clearance and delayed lung aeration result in a delay in the sequence of physiological changes that transform the fetal circulation into a neonatal circuit.[6,63,68] Accordingly, cord clamping is followed by a prolonged period of reduced cardiac output, resulting in gradually worsening of hypoxia and blood pressure fluctuations in the pulmonary and systemic vasculature.

Postnatal LV dysfunction - both systolic and diastolic - adds to the haemodynamic instability during transition in infants with CDH.[40,69] The aetiology of LV dysfunction in CDH is multifactorial and is related to the relatively small size of the LV, resulting from both the herniation of abdominal organs as well as the altered filling haemodynamics.[69-71] After cord clamping, LV dysfunction most likely results from reduced LV filling due to the limited increase in pulmonary blood flow (i.e. preload), LV hypoplasia, and an acute increase in afterload. Moreover, there is transmission of right ventricular dysfunction to the LV via ventricular interdependence.[40,69]

In an ovine CDH model, the lambs developed respiratory acidosis and poor cerebral oxygenation immediately after birth, confirming the hypothesised worsening of hypoxia after immediate cord clamping.[68] Hypoxia may result in an enhanced vasoconstrictive response since the pulmonary vasculature in infants with CDH is hyper-reactive.[68] The resulting increase in vascular resistance could worsen pulmonary hypertension, ultimately leading to an increase in the pre-existing right-to-left shunt, which in turn would aggravate hypoxia and trigger an ongoing cycle of worsening pulmonary hypertension.[6,15,72]

Delivery room management: novel concepts

Timing of cord clamping

The importance of appropriate timing of cord clamping in optimising perinatal stabilisation has been evaluated comprehensively over the last decade.[2,73,74] Delayed cord

clamping (DCC) can be performed using either a 'time-based' or a 'physiological-based' approach, with the latter focussing on the infant and its physiological stability rather than a stopwatch. Indeed, the high variability between infants in their needs and outcomes already suggests that DCC at an arbitrarily chosen time point may not be favourable.[63] The benefits of DCC were initially attributed to an increase in placental transfusion, reducing the incidence of neonatal anaemia in both term and preterm infants.[75,76] In preterm infants the benefit of DCC may however be more related to establishing lung aeration prior to cord clamping, resulting in a smooth cardiopulmonary adaptation at birth.[64] Umbilical cord clamping after the infant has established lung aeration with spontaneous breathing or respiratory support is called physiological-based cord clamping (PBCC).[74,77] Implementing PBCC in the perinatal stabilisation of infants with CDH could hypothetically improve the fetal-to-neonatal transition in these vulnerable infants.

Initial respiratory support

Respiratory support in the delivery room is of major importance for infants with CDH, but it is a double-edged sword as the importance of ventilator-induced lung injury (VILI) and oxygen toxicity is not to be underestimated. Already since decades, 'gentle' ventilation strategies and permissive hypercapnia have been implemented as cornerstones of postnatal management, because less aggressive ventilator strategies could reduce the risk of VILI and oxygen toxicity.[31] However, the optimal way of guiding oxygen supplementation in infants with CDH is still not clear. The possibility of causing inadvertent cerebral hyperoxia was highlighted in a study using an ovine CDH model.[6] The authors hypothesised that this could occur when FiO_2 levels are rapidly increased in response to reduced SpO_2 levels without knowledge of cerebral blood flow, leading to a rapid increase in cerebral oxygen delivery.[6] To directly assess cerebral oxygenation, ventilation management may be better guided by the use of near-infrared spectroscopy.[6]

Current guidelines support immediate intubation in most infants with CDH.[31,61] However, infants predicted to have mild pulmonary hypoplasia are potentially capable of a smooth transition into neonatal life and initiation of invasive respiratory support might actually cause damage to their lungs.[78] To avoid VILI in this specific group of infants with a left-sided defect, intra-abdominal liver, and o/e LHR ≥50%, a trial of spontaneous breathing was postulated in the CDH EURO Consortium guideline.[31,78,79]

The CDH EURO Consortium guideline also recommends that infants with CDH may benefit from starting with FiO_2 levels lower than 100%.[31] While there is minimal evidence to support this recommendation, reduced generation of free radicals associ-

ated with lower FiO_2 levels may prevent subsequent pulmonary vasoconstriction.[80] In a retrospective cohort series that compared starting resuscitation of infants with CDH with FiO_2 50% vs 100%, no differences in immediate postnatal outcomes were found.[81] However, infants who required an increase in FiO_2 during stabilisation were more likely to experience adverse outcomes.[81]

With immediate intubation being the standard of care for most infants with CDH, the time frame between birth and intubation is often limited. This translates into most infants being intubated without any sedation although the negative physiological responses to awake intubation are well-described.[82,83] Ideally, sedation prior to intubation would consist of medication with a rapid time to onset given the urgency to intubate. The limited time frame makes intravenous administration challenging, but alternative methods of administration, such as intranasal, intramuscular, or intrabuccal, potentially have a longer interval to onset of the sedative effect.[84] A better understanding of treatment regimens is an essential first step towards a gentle intubation protocol resulting in minimal stress or pain.

AFTER BIRTH

Placental vasoreactivity

As discussed above, infants with pulmonary hypertension secondary to CDH often fail to adequately respond to vasodilator therapies aiming at reducing the pulmonary vascular resistance.[13] The aetiology of pulmonary hypertension secondary to CDH is not completely understood, but in addition to the reduced arterial cross-sectional area an altered vasoreactive response to stimuli might contribute.[7,85-93] The altered vasoreactive response could originate from several alterations in the pulmonary vasculature, including a decreased expression of endothelial nitric oxide synthase and an increase in phosphodiesterase-5-mediated degradation of cyclic guanine monophosphate.[85-88] Investigation of the underlying vascular alterations is only possible after an invasive lung biopsy, which cannot be done routinely in alive infants, hence an alternative is warranted. In accordance with alterations in placental vasoreactivity in pre-eclamptic women,[94-96] one could hypothesise that the fetoplacental vasculature may be used as a proxy as it is exposed to the same circulating factors in the fetal circulation and it demonstrates similar responses to stimuli such as hypoxia-induced vasoconstriction.[97-107] The potential similarities between fetoplacental and pulmonary vessels have not been investigated yet, but if this hypothesis is correct this could prove a major step towards individualised postnatal management.

Tidal volume

The variability in underlying disease severity results in a large interpatient variation in the clinical presentation of postnatal problems such as pulmonary hypertension. Infant-specific parameters could enable individualised management on the intensive care unit, preferably by early identification of those infants with the highest risk of clinical deterioration. The fetal-to-neonatal stabilisation period potentially provides such parameters and in a prospective study tidal volumes of spontaneous breaths during stabilisation were associated with mortality, chronic lung disease, and the need for iNO.[108] However, tidal volume was correlated with the o/e LHR and was therefore not considered an independent predictor of outcomes.[108] Still, parameters collected during stabilisation might provide a useful reflection of disease severity at birth.[108]

Oxygen saturation index

The oxygenation index (OI) is a value calculated to estimate the severity of respiratory failure and it predicts mortality in infants with CDH.[109,110] Calculating the OI requires the arterial pO_2 value, which is obtained by means of arterial blood gas sampling. As most infants with CDH have a patent ductus arteriosus at this time and preductal arterial pO_2 values are thus higher than postductal arterial pO_2 values, the site of blood gas sampling influences the calculated OI.[40] Moreover, arterial blood gas sampling is invasive, requiring an arterial line or intermittent arterial puncture.[111] The non-invasively measured oxygen saturation index (OSI) could potentially alleviate some disadvantages of the OI, although its use in infants with CDH has not been established yet.[111]

AIMS AND SCOPE OF THIS THESIS

Based on the above-mentioned aspects of perinatal care in infants with CDH, the research projects that are part of this thesis aimed at:

- Refining parental counselling before birth (**Part I**);
- Optimising the fetal-to-neonatal transition at birth (**Part II**);
- Individualising care after birth (**Part III**).

PART I | BEFORE BIRTH

We aimed at refining parental counselling by evaluating which factors affect parents in deciding whether to terminate the pregnancy in case of fetal CDH (**chapter 2**) and

by evaluating the associations between prenatal ultrasound markers and survival at discharge in very preterm born infants with CDH (**chapter 3**).

PART II | AT BIRTH

In this part, we evaluated key aspects of current delivery room management. In **chapter 4** we assessed whether DCC for three minutes during caesarean sections results in an increase in maternal bleeding complications. The effects of implementation of PBCC on the occurrence of pulmonary hypertension in the first 24 hours after birth in infants with CDH are currently being investigated within a multicentre randomised controlled trial and the study protocol is provided in **chapter 5. Chapter 6** discusses the outcomes of infants with CDH and estimated mild pulmonary hypoplasia stabilised according to a spontaneous breathing approach. Based on this experience and an expert panel discussion, we have developed a standardised resuscitation algorithm for a spontaneous breathing approach (**chapter 7**). **Chapter 8** illustrates the international variation in pre-intubation medication in infants with CDH.

PART III | AFTER BIRTH

We also focussed on individualising postnatal treatment. **Chapter 9** demonstrates differences in fetoplacental vasoreactivity between healthy and CDH placentas. We evaluated the correlation and association between OI and OSI after birth in **chapter 10**. **Chapter 11** discusses the follow-up study on the use of continuous OSI measurements as early predictor of a complicated postnatal course.

PART IV | SUMMARY AND DISCUSSION

The results of each chapter are summarised in **chapter 12 and 13** and this thesis concludes with a general discussion and directions for future research in **chapter 14**.

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PART I

| Before birth |

2 | Termination of pregnancy after a prenatal diagnosis of congenital diaphragmatic hernia: factors influencing the parental decision process

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ABSTRACT

Objective: To evaluate the incidence of termination of pregnancies (TOP) and factors associated with the decision for TOP in prenatally detected congenital diaphragmatic hernia (CDH).

Study Design: Single-centre retrospective cohort includes all prenatally detected CDH cases born between January 2009 and December 2021. Parental factors, such as parity, and fetal characteristics, such as disease severity, were collected. Descriptive statistics were used to present the data. Differences between terminated and continued pregnancies were analysed.

Results: The study population consisted of 278 prenatally detected CDH cases of which 80% detected <24 weeks of gestation. The TOP rate was 28% in cases that were detected <24 weeks of gestation. Twenty continued pregnancies resulted in either intrauterine fetal demise (n=6), preterm birth <24 weeks (n=2), or comfort care after birth (n=12). The survival rate was 70% in the remaining 195 live born cases. Factors associated with the decision for TOP were additional fetal genetic or anatomical abnormalities (p<0.0001) and expected severity of pulmonary hypoplasia in left-sided CDH (p=0.0456).

Conclusion: The decision to terminate a pregnancy complicated by fetal CDH depends on the severity of pulmonary hypoplasia and presence of additional abnormalities. This emphasises the importance of early referral to expertise centres for detailed evaluation and multidisciplinary counselling.

INTRODUCTION

The implementation of routine prenatal ultrasound screening programs in combination with technological improvements in scanning equipment has led to an increase in the prenatal detection rate of congenital birth defects.[1] Currently, around 70% of all cases with a congenital diaphragmatic hernia (CDH) are detected before birth, of which 3-29% in the first trimester, 58-72% in the second trimester, and 8-25% in the third trimester.[1-3] Early detection of congenital malformations provides parents an opportunity to reflect on whether to continue the pregnancy or not. Legislation in the Netherlands obligates that a decision to end the pregnancy must be made prior to 24 weeks of gestation with an exception for conditions that have an unquestionable lethality after birth. However, late termination of pregnancy (TOP) in the latter group is rarely done because of stringent administrative procedures and post-hoc ethical review.

The reported TOP rates for CDH cases vary between historical cohorts from different countries with observations ranging between 6% and 100%.[2,4-13] This large variation is partly explained by differences in study populations as the TOP rate is lower in populations that include cases in which TOP was no longer an option due to a late diagnosis.

Specific fetal characteristics are associated with adverse outcomes for infants with CDH, such as gestational age at diagnosis[1], additional genetic or anatomical abnormalities[14-16], a right-sided defect[15,17-20], expected severe lung hypoplasia (determined with ultrasound or fetal magnetic resonance imaging)[21], and intrathoracic liver position[18,21-24]. These disease-related factors might play a role for families when deciding to either continue or terminate the pregnancy, as was observed in other fetal abnormalities.[25-29] Parental characteristics on the other hand, such as maternal age, parity, ethnicity, and socioeconomic factors, might also play a role.[26,27,30-33] In this single-centre retrospective study, we describe a cohort of prenatally detected CDH patients and evaluate fetal and parental factors that may be associated with deciding to discontinue the pregnancy.

METHODS

This is a single-centre retrospective cohort study performed at Erasmus MC, University Medical Centre Rotterdam, The Netherlands, a national and level 3 referral centre. Data were retrospectively extracted from the medical files of consecutive cases evaluated at our centre between January 2009 and December 2021. The study population consisted of all cases with a prenatal diagnosis of CDH that received prenatal counselling and

for whom birth and postnatal management were planned at our centre. The research protocol was approved by the medical ethical committee (METC 2022-0340) of the Erasmus MC and informed consent was waived due to the retrospective study design.

The following maternal data were collected: age at delivery, mode of conception (spontaneous or assisted), parity, ethnic background (Caucasian or other), socioeconomic status (low, middle or high), and relationship status. Socioeconomic status was defined by maternal educational level: low (no education, primary school, and lower vocational training), middle (intermediate vocational training), or high (higher vocational training or university). Fetal characteristics concerned gestational age at diagnosis or at first visit to our centre, side of the hernia (left or right), observed to expected lung-to-head ratio (o/e LHR) and gestational age at measurement, liver position (intra-abdominal or intrathoracic), additional anatomical and genetic abnormalities detected before 24 weeks of gestation, fetal surgery, and gestational age at birth. Fetal surgery in the form of tracheal occlusion was offered to parents throughout the entire study period. Neonatal outcomes included overall mortality and neonatal death (death within the first 28 days after birth). If possible, we collected the o/e LHR measurement that was used for the prenatal counselling. Left-sided CDH cases were divided in expected *mild* (o/e LHR 35.0-44.9% with intra-abdominal liver, or o/e LHR ≥45.0%, irrespective of liver position), *moderate* (o/e LHR 25.0-34.9%, irrespective of liver position, or o/e LHR 35.0-44.9% with intrathoracic liver), or *severe* (o/e LHR <25.0%, irrespective of liver position) pulmonary hypoplasia.[21,34] Right-sided CDH cases were divided in expected *moderate* (o/e LHR ≥50.0%) or *severe* (o/e LHR <50.0) pulmonary hypoplasia.[17,20]

Normality of the data was checked with QQ-plots and density distributions combined with the Shapiro-Wilk test. Continuous data were presented as mean ± standard deviation or median [interquartile range], depending on whether the data were normally distributed. Categorical data were presented as absolute numbers and percentages. Statistical tests for continuous data were the Mann-Whitney *U* test (non-parametric) and the Student *t* test (parametric). Categorical variables were analysed with a chi-squared test or Fisher exact test. Statistical analysis was done using R (R Core Team, 2020). $P<0.05$ was considered statistically significant.

RESULTS

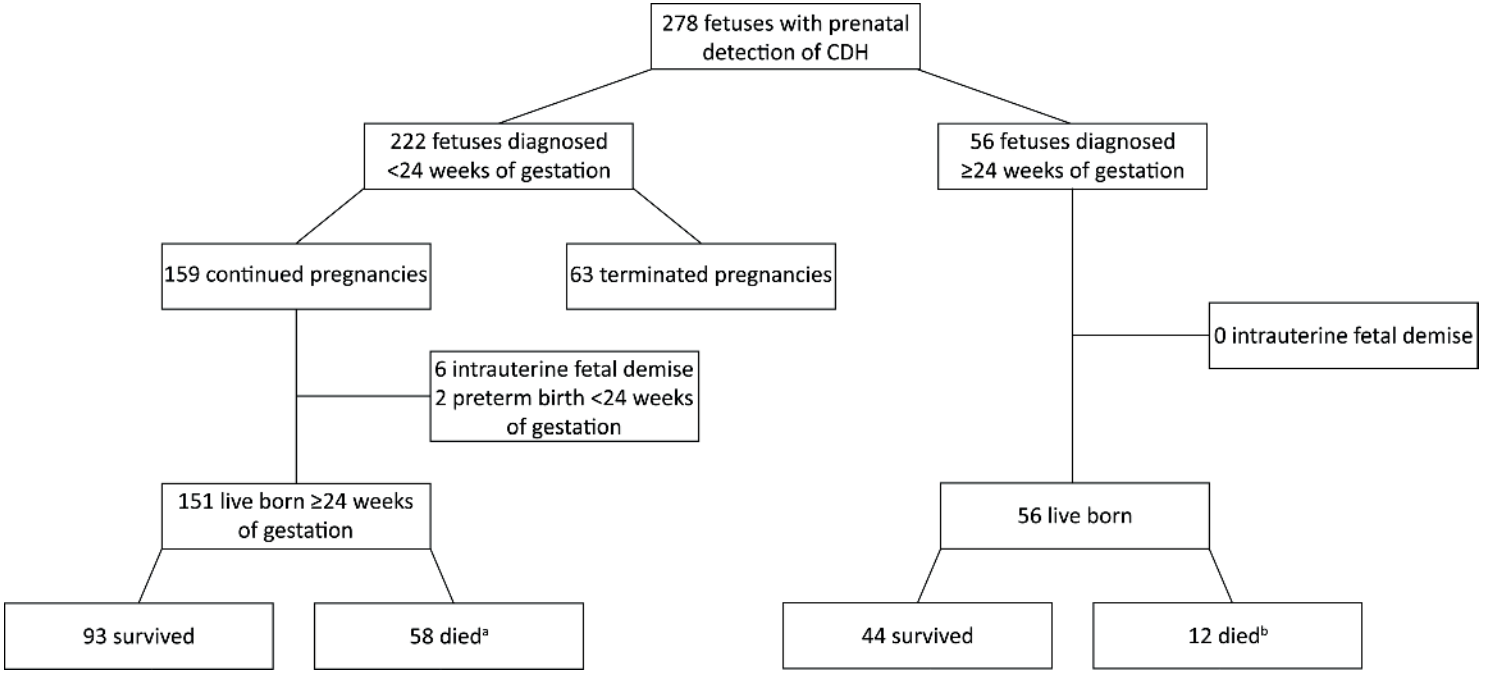
A total of 278 pregnancies with a prenatal diagnosis of a CDH were included (Figure 1). Eighty percent (n=222) were detected before 24 weeks of gestation (*early* diagnosis). In *early* diagnosed cases, the expected severity of pulmonary hypoplasia was mild in

41% (n=90), moderate in 34% (n=76), and severe in 18% (n=41). In a small proportion of cases (7%, n=15), the o/e LHR could not be determined because of early gestational age. In cases diagnosed ≥24 weeks of gestation (*late* diagnosis), the expected severity of pulmonary hypoplasia was mild in 55% (n=31), moderate in 27% (n=15), and severe in 18% (n=10). Prenatal treatment in the form of fetoscopic endoluminal tracheal occlusion (FETO) was attempted in 11 early diagnosed cases, but in one case, it was not possible to position the tracheal balloon correctly.

The TOP rate was 28% (63/222) in all *early* diagnosed cases and 23% (63/278) in the entire study population. Figure 2 demonstrates the TOP rate per year in all *early* diagnosed cases, ranging between 0% and 54%. Of 215 continued pregnancies, 6 pregnancies resulted in intrauterine fetal demise, 2 pregnancies resulted in preterm birth prior to 24 weeks of gestation, and in 12 pregnancies, the infants received comfort care after birth. The majority (n=10) of these infants receiving comfort care were diagnosed with additional abnormalities before 24 weeks of gestation, but parents refrained from TOP. Additionally, 1 infant with isolated CDH was born very preterm (24^{+5} weeks of gestation) and received comfort care because of that. The remaining 195 infants were born at a median gestational age of 38^{+1} [37^{+1}-38^{+4}] weeks, reflecting the standard of care in our centre with induction of labour around 38 weeks of gestation. The overall survival rate in live born cases receiving active management after birth was 70% (137/195), with non-surviving infants dying on a median of day 12 [2-33]; the majority (67%) already died within the first 28 days after birth. The expected severity of pulmonary hypoplasia in non-surviving infants was mild in 21% (n=12), moderate in 43% (n=25), and severe in 36% (n=21).

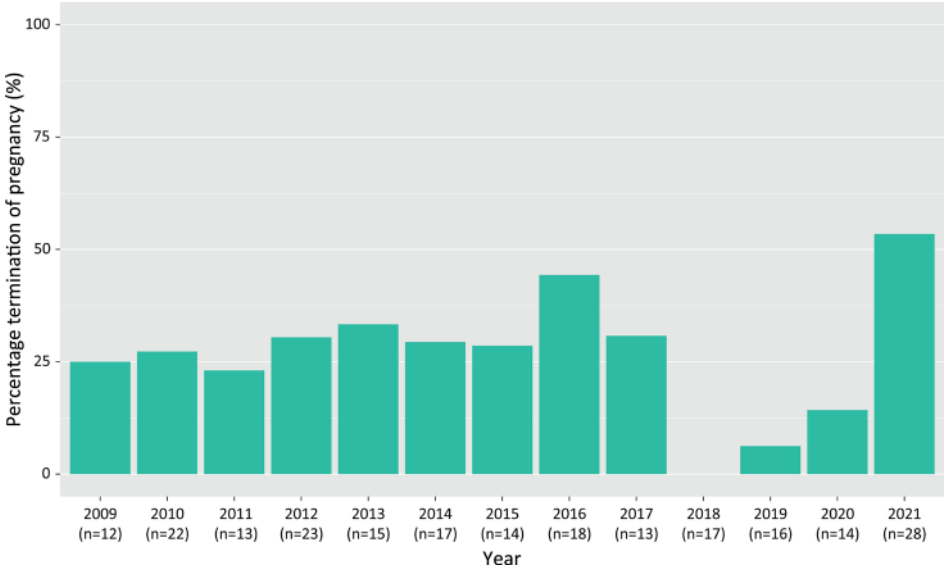
Table 1 depicts the characteristics for both terminated pregnancies and continued pregnancies in *early* diagnosed cases. Despite numerical differences, no significant differences were observed in parental factors. The odds of pregnancy termination were higher for cases with at least one additional abnormality (OR 7.78; 95% CI [4.03-15.00]; $p<0.0001$). In left-sided CDH, o/e LHR was significantly lower in terminated pregnancies (35% [29-40%] *vs* 42% [33-50%], $p=0.00372$), but liver position was not significantly different between terminated and continued pregnancies (intrathoracic liver position in 46% *vs* 49%, $p=0.895$). The expected severity of pulmonary hypoplasia in left-sided CDH, combining liver position and o/e LHR, was significantly different between the two groups ($p=0.0456$) with a higher percentage of moderate (50% *vs* 36%) and severe (16% *vs* 9%) pulmonary hypoplasia in the group with terminated pregnancies. In right-sided CDH, o/e LHR was not significantly different (48% [42-50%] *vs* 35% [28-49%], $p=0.159$). In the total study population, the TOP rates per severity group were 17% for mild CDH, 30% for moderate CDH, and 34% for severe CDH.

Figure 1 Flowchart of study population. CDH: congenital diaphragmatic hernia.



[a] 9 infants received comfort care after birth. [b] 3 infants received comfort care after birth.

Figure 2 Termination of pregnancy rates in early (<24 weeks of gestation) detected congenital diaphragmatic hernia.



Numbers of early detected congenital diaphragmatic hernia cases per year are depicted between brackets.

Table 1 Characteristics of terminated and continued pregnancies in early (<24 weeks of gestation) detected congenital diaphragmatic hernia

	Terminated pregnancies		Continued pregnancies		*p*
	n	(n=63)	n	(n=159)	
Maternal age at delivery (years)	63	32 ± 5	159	31 ± 6	0.487
Nulliparous women	63	29 (46)	159	83 (52)	0.497
Spontaneous conception	61	52 (85)	158	146 (92)	0.175
Caucasian	58	43 (74)	158	103 (65)	0.280
Socioeconomic status	35		131		0.664
Low		10 (29)		48 (37)	
Middle		14 (40)		45 (34)	
High		11 (31)		38 (29)	
Single mothers	63	2 (3)	159	4 (3)	1
Gestational age at diagnosis diaphragmatic defect (weeks^{+days})	63	20^{+1} [19^{+1}-21^{+1}]	159	20^{+4} [20^{+0}-21^{+1}]	0.061
Left-sided defect	61	52 (85)	157	138 (88)	0.764
Additional abnormalities	63	38 (60)	159	26 (16)	<0.0001
Anatomic		33 (52)		20 (13)	
Genetic		22 (35)		14 (9)	
Both anatomic and genetic		16 (25)		6 (4)	

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

DISCUSSION

To the best of our knowledge, this is the first series that evaluated factors associated with the parental decision to discontinue the pregnancy in case of a CDH. In this study, we observed that around one fourth of parents decided not to continue the pregnancy. Factors associated with the decision of terminating the pregnancy were the expected severity of pulmonary hypoplasia in left-sided CDH and the presence of additional abnormalities.

Previous series have observed that the presence of additional anatomical and/or genetic abnormalities influences the parental decision on TOP in fetuses with CDH with TOP rates of 6-19% for isolated CDH cases and 35-61% for non-isolated cases.[7,13,35] The findings in our cohort reconfirm this, observing a threefold increase in TOP (16% *vs* 59%) in non-isolated CDH cases, highlighting the importance of prenatal genetic testing and expert ultrasound examination. On the other hand, genetic testing is rapidly progressing to whole exome sequencing or even whole genome sequencing for any congenital abnormality. This in turn will increase the yield in detecting potential genetic aberrations of unknown significance; yet the challenge is to determine the clinical relevance of each of these incidental findings.[36,37] The clinical implications of these variants of unknown significance should be further assessed using international databases, aiming at aiding parents in making decisions about the current but also future pregnancies.[38]

As expected based on historical literature in other fetal conditions, disease severity seems to be a factor in parental decision-making.[25,26,28,33] In CDH, disease severity is estimated based on the combination of side of the defect, position of the liver, and estimated lung size. Although we did not find significant differences in the first two respective factors, the combination of side of the defect, position of the liver, and estimated lung size was significantly different in left-sided CDH with a lower incidence of mild and higher incidences of moderate and severe pulmonary hypoplasia in terminated pregnancies.

The option of fetal therapy was discussed with families during the whole study period; yet until 2020, this was only offered within a randomised trial and participation required temporary relocation to a FETO centre abroad. It is unfortunately impossible to determine whether these considerations may have influenced the decision process. With the recently proven benefits of fetal therapy for isolated cases with severe pulmonary hypoplasia and minimal maternal risks, we speculate that more parents will opt for fetal therapy, which may affect the TOP rate in this subgroup.[39]

On the other hand, despite improved survival rates, infants with severe CDH will still need a lengthy period of intensive care and complications are not uncommon. The psychological and social impact of this prolonged period of uncertainty and anxiety on the whole family should not be underestimated, and for some parents, this will be the main consideration to discontinue the pregnancy.

Clinically relevant differences have been demonstrated between disease severity assessment in referring hospitals and expertise referral centres.[10] In case of a prenatal diagnosis of a CDH, prompt referral to a specialised centre with an experience in both prenatal and postnatal care of CDH would therefore provide parents with the much needed comprehensive and reliable information.[40] Thus, healthcare professionals should be cautious when counselling parents without having consulted a healthcare professional with expertise on CDH.[10,41] Moreover, to ensure parental wellbeing, psychosocial support should be integrated in the prenatal trajectory.[40]

Routinely, a structural ultrasonographic examination is offered to all pregnant women in the Netherlands around 20 weeks of gestation. However, a 13-weeks ultrasound has recently (2021) become available as part of an implementation study (Implementation of first Trimester Anomaly Scan [IMITAS-study]), potentially resulting in an earlier gestational age at diagnosis. As there is evidence that early TOP is less traumatic for the parents, this is certainly interesting for women expecting a child with CDH.[42] On the other hand, earlier studies have observed relatively low detection rates of CDH in the first trimester; hence the effect of implementing a routine 13-weeks screening ultrasound on the incidence of TOP is uncertain.[3]

In contrast to previous series, we could not confirm parental factors that were significantly associated with TOP.[27] Despite an apparent higher parity of mothers in the TOP-group, this difference did not reach significance, underlining conflicting results in earlier studies.[31]

In our cohort, the survival rate was 49% (137/278) in the entire study population, 64% (137/215) in all continued pregnancies, and 70% (137/195) in all live born cases receiving active postnatal management. These different survival rates reflect the hidden mortality when only the survival rate in live born cases is reported. It should be noted that our single-centre results may not be representative of other centres or countries due to differences in regulations regarding pregnancy termination, cultural or religious influences, and prenatal counselling.[27] We speculate that our cohort depicts an overall lesser severity of pulmonary hypoplasia in live born cases than other centres, due to the higher likelihood of severe cases to be terminated.[43,44] On the

other hand, the improvement in survival of infants with CDH in the past decades might have resulted in a tendency for women to continue their pregnancy.[7] However, in our single-centre series, we could not determine any trend in TOP rates.

Interestingly, we observed lower TOP rates between 2018 and 2020. These lower TOP rates may be due to an increased number of intrauterine fetal demise, preterm birth prior to 24 weeks of gestation, and comfort care after birth in these specific years. Indeed, 4 of 6 cases resulting in intrauterine fetal demise, 1 of 2 cases resulting in preterm birth prior to 24 weeks of gestation, and 4 of 9 cases receiving comfort care after birth concerned pregnancies in 2018-2020. Another explanation might be the estimated severity of pulmonary hypoplasia. This could particularly be the case in 2019, as we did not have any case with expected *severe* pulmonary hypoplasia in that year.

Unfortunately, we were unable to retrieve data on the exact process of parental decision-making, and thus, we should be cautious in drawing firm conclusions. In this study, we opted not to use parental questionnaires as we expected both recall bias and selection bias due to more responses from parents that continued their pregnancies or from parents that have only recently been confronted with a prenatal diagnosis of CDH. Another limitation of this retrospective study is that we were unable to adjust for the influence of counselling by specific healthcare professionals.[45] However, parental counselling in our centre is routinely performed by both a maternal-fetal medicine specialist and a paediatric specialist, and thus, we believe that this influence is limited. Although it is standard of care to refer parents with a fetal diagnosis of CDH to an expertise centre, we cannot rule out the possibility of other centres performing TOP in prenatally diagnosed CDH without referral. Thus, our estimated TOP rate might be a slight underestimation. As already mentioned, the single-centre study design hampers translation of our results to other centres.

CONCLUSIONS

Parental decision-making on whether to continue or terminate a pregnancy with a fetal diagnosis of CDH is a delicate process that is mainly influenced by fetal disease severity and the presence of additional fetal abnormalities. To guarantee counselling of parents with reliable information on disease severity, we advise that parental counselling should be carried out in dedicated referral centres with multidisciplinary expertise on these important prenatal factors.

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3 | Survival in very preterm infants with congenital diaphragmatic hernia and association with prenatal imaging markers: a retrospective cohort study

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ABSTRACT

Objectives: To describe the outcomes of preterm born infants with congenital diaphragmatic hernia (CDH; ≤32.0 weeks of gestation) and the associations between prenatal imaging markers and survival.

Design: Retrospective cohort study.

Setting: Multicentre study in large referral centres.

Population: Infants with an isolated unilateral CDH, live born at 32.0 weeks or less of gestation, between January 2009 and January 2020.

Methods: Neonatal outcomes were evaluated for infants that were expectantly managed during pregnancy and infants that underwent fetoscopic endoluminal tracheal occlusion (FETO) therapy, separately. We evaluated the association between prenatal imaging markers and survival to discharge. Prenatal imaging markers included observed to expected lung-to-head ratio (o/e LHR), side of the defect, liver position, stomach position grade, and observed to expected total fetal lung volume (o/e TFLV) with survival.

Main Outcome Measure: Survival to discharge.

Results: We included 53 infants born at 30^{+4} [IQR 29^{+1}-31^{+2}] weeks. Survival in fetuses expectantly managed during pregnancy was 48% (13/27) in left-sided CDH and 33% (2/6) in right-sided CDH. Survival in fetuses that underwent FETO therapy was 50% (6/12) in left-sided CDH and 25% (2/8) in right-sided CDH. The o/e LHR at baseline was positively associated with survival in cases expectantly managed during pregnancy (odds ratio [OR] 1.20, 95% CI 1.07-1.42, $p<0.01$), but not in cases that received FETO therapy (OR 1.01, 95% CI 0.88-1.15, $p=0.87$). Stomach position grade ($p=0.03$) and o/e TFLV were associated with survival ($p=0.02$); liver position was not ($p=0.13$).

Conclusions: In infants with CDH born at or before 32 weeks of gestation, prenatal imaging markers of disease severity were associated with postnatal survival.

INTRODUCTION

The risk of preterm birth (<37 weeks of gestation) is higher in fetuses with a congenital diaphragmatic hernia (CDH) than in fetuses without any malformations (22-35% vs 9.7%).[1-7] One could expect an increase in the incidence of preterm birth as prenatal surgery in the form of fetoscopic endoluminal tracheal occlusion (FETO) is now a valid option in the severest cases.[6] Both CDH and prematurity are associated with postnatal problems, hence the CDH-related risk of mortality will probably increase if combined with prematurity-related morbidity.[4,8-10] This was clearly demonstrated by data from the CDH study group registry, showing a positive relationship between survival rate and gestational age at birth irrespective of other factors: 38% in very preterm infants (≤32 weeks), 57% in moderate and late preterm infants (32-37 weeks), and 73% in term infants.[4]

Survival in CDH is mainly determined by the severity of pulmonary hypoplasia, as it correlates with respiratory insufficiency and pulmonary hypertension after birth.[11] During pregnancy, the best validated method to assess the severity of pulmonary hypoplasia is the observed to expected lung-to-head ratio (o/e LHR) determined on a two-dimensional ultrasound image of the contralateral lung.[8] In left-sided CDH, this is often combined with evaluation of the liver position.[8,12,13] Alternative parameters are the observed to expected total fetal lung volume (o/e TFLV) by means of magnetic resonance imaging (MRI) volumetry or the grading of stomach position with ultrasound.[14-18] It could be hypothesised that prematurity-related morbidity attenuates the existing association between prenatal ultrasound markers and CDH-related mortality.[8] This study therefore aimed to describe the outcomes of infants with a CDH born at or before 32.0 weeks of gestation, and the associations between currently used prenatal imaging markers and FETO therapy against the outcome of survival.

METHODS

Study population

We performed a retrospective cohort study in seven large referral centres experienced with the assessment and management of CDH in the prenatal period. These centres adhere to standardised international consensus guidelines for postnatal management and participated in the Tracheal Occlusion to Accelerate Lung Growth (TOTAL) trials.[5,6,12,19] We included all consecutive infants with unilateral CDH who were live born at or before 32.0 weeks of gestation between January 2009 and January 2020, and had no associated major structural or genetic abnormalities diagnosed either before or

after birth. Further exclusion criteria included infants planned for postnatal palliative care and infants without prenatal measurement of o/e LHR.

Baseline characteristics

Maternal and neonatal baseline characteristics were collected from hospital records. Fetal growth restriction was defined as (1) fetal abdominal circumference (AC) or estimated fetal weight (EFW) below the third centile, or (2) absent end-diastolic flow in the umbilical artery, or (3) AC/EFW below the tenth centile combined with uterine artery pulsatility index greater than the 95th centile and/or umbilical artery pulsatility index greater than the 95th centile.[20] We recorded whether fetuses were expectantly managed during pregnancy or underwent FETO. FETO therapy was considered in fetuses in the following subgroups: (1) left-sided CDH, o/e LHR 25% or less, irrespective of liver position; (2) left-sided CDH, o/e LHR 26-35%, irrespective of liver position; (3) left-sided CDH, o/e LHR 36-45% with intrathoracic liver, and (4) right-sided CDH, o/e LHR 45% or less with intrathoracic liver.[5,6] Probably as a result of the preliminary results of Russo *et al*,[21] one fetus with right-sided CDH and o/e LHR of 49% received FETO therapy as well.

Prenatal predictors

Prenatal ultrasound markers included the o/e LHR value, which was used for prenatal counselling, side of the defect, liver position, and stomach position grade. Also, the o/e TFLV was measured on MRI. The o/e LHR was measured by experienced sonographers using either the tracing or longest axis method, normalised to a gestational age reference value according to a standardised protocol.[22] Subgroups for left-sided CDH were: o/e LHR up to 25%, o/e LHR 26-35%, o/e LHR 36-45%, and o/e LHR greater than 45%.[8] Subgroups for right-sided CDH were o/e LHR up to 50% and o/e LHR greater than 50%.[21] Liver position and stomach position grade were only reported in left-sided CDH. Liver position was either intra-abdominal (down) or intrathoracic (up). The axial plane at the level of the four-chamber view of the heart was used to evaluate stomach position grade, which was graded according to Cordier *et al*.[14,22] Stomach position is graded as follows: Grade 1, stomach not visualised; Grade 2, stomach visualised anteriorly, next to the apex of the heart, with no structure between stomach and sternum; Grade 3, stomach visualised along from the apex of the heart and abdominal structures anteriorly; or Grade 4, Grade 3 with stomach posterior to the level of the atrioventricular heart valves.[14]

Outcome measures

The primary outcome of interest was survival to discharge from the intensive care unit (ICU). Secondary outcomes were occurrence of pulmonary hypertension at any

point during ICU admission (mild: right ventricular systolic pressure [RVSP]/systolic blood pressure [SBP] <2/3; moderate: RVSP/SBP 2/3-1; severe: RVSP/SBP >1),[23] pulmonary hypertension treatment with inhaled nitric oxide and/or sildenafil, use of extracorporeal membrane oxygenation (ECMO) therapy, number of days on mechanical ventilation, and presence of bronchopulmonary dysplasia (which was assessed at a postmenstrual age of 36 weeks using the criteria from Jobe *et al.*[24]).

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median [interquartile range] depending on the distribution. Categorical data are expressed as absolute number (n) and percentage (%). Odds ratios (OR) and corresponding 95% CI were calculated for risk factors for preterm birth that have an incidence of at least 10% in our data. Continuous data were analysed using the Mann-Whitney *U* test or one-way analysis of variance test and categorical variables were analysed using the Fisher exact test. The area under the receiver operating characteristic curve was used to evaluate the discriminative ability of o/e LHR for survival in infants with left-sided CDH expectantly managed during pregnancy. The optimal cut-off was calculated with the Youden index, which gives equal weight to sensitivity and specificity, by using the R package 'cutpointr'.

Logistic regression analyses evaluated the association between selected covariates and the outcome of interest; survival to discharge. We selected the following covariates based on clinical relevance and literature: o/e LHR, side of the defect, and FETO therapy. As a result of the limited sample size, we were not able to include additional covariates. Univariate logistic regression was used to test the main effects of the selected covariates in specified subgroups: all infants, infants with left-sided CDH, infants with right-sided CDH, infants expectantly managed during pregnancy, and infants that underwent FETO therapy. Multivariable logistic regression was used to test the linearity of o/e LHR and interactions between covariates, because we expected o/e LHR and FETO therapy to have an interaction. The choice of model is based on clinical insight along with the Akaike information criterion (AIC), which selects the model with the lowest AIC as the best fitting model. The effect estimates are reported as OR [95% CI]. For interaction terms that include the o/e LHR, a continuous variable, effect estimates are reported at clinically relevant o/e LHR cut-offs.

The statistical analyses were designed and performed in collaboration with the Department of Epidemiology & Biostatistics of the Erasmus MC University Medical Center. We analysed the data using the statistical software of R (R Core Team [2020], Vienna, Austria, v4.1.1). A value of *p* less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

In total, 53 infants were included with a median gestational age at birth of 30^{+4} [29^{+1}-31^{+2}] weeks. Mean maternal age at time of delivery was 31±5 years and 27 women were nulliparous. Three fetuses were diagnosed with minor genetic or anatomical abnormalities, which were deemed unlikely to influence outcomes (one with mega-ureter, one with low-grade mosaicism of chromosome 4 without any other phenotypic anomalies than CDH, and one with bilateral clubfeet). Baseline characteristics for expectantly managed fetuses are depicted in Table 1. In infants expectantly managed before birth, we did not find differences in odds of mortality between infants with and without known risk factors concerning preterm birth (i.e. amniocentesis, pre-existing maternal disease, intra-uterine infection, polyhydramnios, and preterm premature rupture of the membranes; Supplementary Table 1). The ORs of mortality associated with smoking during pregnancy, history of preterm birth, maternal sepsis, and oligohydramnios are not reported because of low incidences (<10%) in this study population.

Table 1 Baseline characteristics of preterm born infants with CDH

	Left-sided CDH		Right-sided CDH	
	n	(n=27)	n	(n=6)
o/e LHR (%)	27	33 [29-42]	6	35 [29-41]
Gestational age at measurement o/e LHR (weeks^{+days})	27	25^{+4} [23^{+0}-27^{+4}]	6	26^{+2} [24^{+2}-27^{+5}]
o/e TFLV (%)	17	30 [24-34]	3	25 [20-27]
Gestational age at measurement o/e TFLV (weeks^{+days})	11	25^{+5} [24^{+4}-27^{+0}]	5	27^{+4} [26^{+0}-28^{+3}]
Intrathoracic liver position	27	15 (56%)	6	6 (100%)
Stomach position	18		6	
Grade 1		3 (12%)		6 (100%)
Grade 2		8 (31%)		0
Grade 3		6 (23%)		0
Grade 4		9 (35%)		0
Fetal growth restriction	27	3 (11%)	6	0
Prenatal corticosteroids	27	27 (100%)	6	5 (83%)
Vaginal birth	27	14 (52%)	6	1 (17%)
Gestational age at birth (weeks^{+days})	27	29^{+4} [27^{+6}-30^{+6}]	6	29^{+5} [29^{+2}-30^{+5}]
Male	27	16 (59%)	6	4 (67%)
Birth weight (g)	27	1250 [955-1470]	6	1385 [1195-1579]
Apgar 5'	23	6 [5-8]	6	7 [5-8]
Umbilical artery pH	15	7.30 [7.26-7.37]	5	7.41 [7.23-7.42]

Data are expressed as median [interquartile range] or n (%).
CDH: congenital diaphragmatic hernia; FETO: fetoscopic endoluminal tracheal occlusion; o/e LHR: observed to expected lung-to-head ratio; o/e TFLV: observed to expected total fetal lung volume.

Left-sided CDH expectantly managed during pregnancy

In left-sided CDH (n=27), median o/e LHR was 33% [29-42%]. The survival rate was 48% (13/27) and non-surviving infants died at a median of day 2 [1-9]. All surviving infants and two non-surviving infants underwent surgical correction of the defect at day 6 [3-7], and 87% (13/15) required patch repair. Pulmonary hypertension was diagnosed in 24 (89%) infants on day 1 [1-1]. In two survivors, no signs of pulmonary hypertension were present, whereas the presence of pulmonary hypertension was not evaluated in one non-survivor because death occurred before evaluation. Treatment of pulmonary hypertension consisted of inhaled nitric oxide in 21 infants, of whom 9 infants were also treated with sildenafil. One infant born at a gestational age of 31^{+6} weeks received ECMO therapy; the cannulas were placed at 46 hours of life and the ECMO run lasted until death at 23 days. Surfactant was administered in 21 infants. Mechanical ventilation was provided for 21 [9-23] days in surviving infants. The prevalence of prematurity-related morbidity was as follows: necrotising enterocolitis in one infant, retinopathy of prematurity stage ≥3 in two infants, intraventricular haemorrhage in eight infants, sepsis confirmed with blood culture in nine infants, and bronchopulmonary dysplasia in twelve infants. Survivors were admitted to the ICU for 69 [43-101] days. Four infants required supplemental oxygen after discharge.

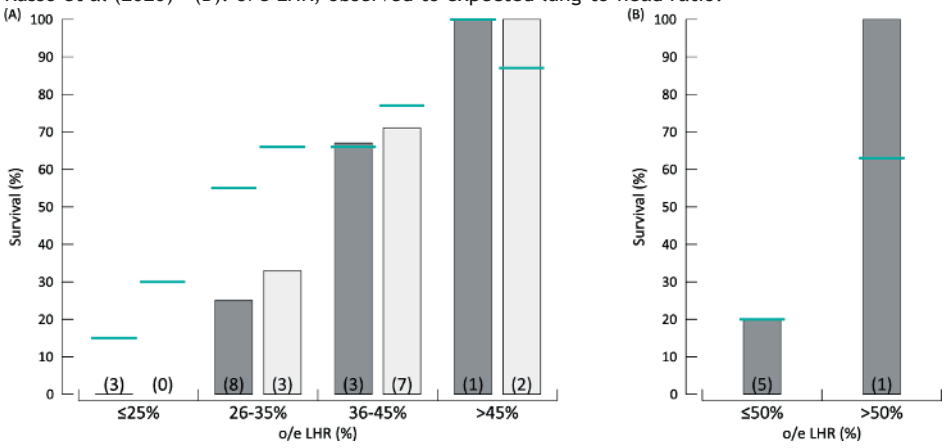
Stomach position grade was significantly associated with survival (grade 1: 3/3 [100%], grade 2: 5/8 [63%], grade 3: 3/6 [50%], and grade 4: 1/9 [11%], stomach grade missing n=1; p=0.03). Also, a higher stomach position grade was associated with a lower o/e LHR (p<0.001). In contrast, dichotomously measured liver position was not significantly associated with survival (intra-abdominal liver 8/12 [67%] and intrathoracic liver 5/15 [33%], p=0.13). The o/e TFLV was significantly higher in survivors than in non-survivors (36% [31-40%] vs 28% [23-31%], p=0.02). The association between o/e LHR and survival is depicted in Figure 1. The area under the receiver operating characteristic curve for prediction of survival to discharge from the o/e LHR was 0.87. The optimal cut-off, defined by highest sensitivity and specificity, for the o/e LHR to predict survival was 42%, with a sensitivity of 62% and specificity of 100%.

Right-sided CDH expectantly managed during pregnancy

In right-sided CDH (n=6), median o/e LHR was 35% [29-41%]. The survival rate was 33% (2/6) and non-surviving infants died at a median of day 16 [1-85]. Four infants underwent surgical correction of the defect at day 5 [4-6], and 75% required patch repair. Pulmonary hypertension was diagnosed in 5 (83%) infants on day 1 [1-1]. Treatment consisted of inhaled nitric oxide in four infants, of whom three infants were also treated with sildenafil. Surfactant was administered in four infants. Mechanical ventilation was provided for 19 [3-39] days. The prevalence of prematurity-related

morbidity was as follows: necrotising enterocolitis and retinopathy of prematurity stage ≥3 in zero infants, intraventricular haemorrhage in one infant, sepsis confirmed with blood culture in three infants, and bronchopulmonary dysplasia in four infants. Infants were admitted to the ICU for 42 [9-92] days. The association between o/e LHR and survival is depicted in Figure 1. Due to the limited number of right-sided CDH cases, we did not evaluate the association between additional prenatal markers and survival in this group.

Figure 1 Survival rates for each severity group in infants that received expectant prenatal management with left-sided (A) and right-sided (B) congenital diaphragmatic hernia and were born ≤32.0 weeks of gestation. The filled bars represent fetuses with intrathoracic liver position and the open bars represent fetuses with intra-abdominal liver position. Numbers per group are depicted between brackets. The solid lines represent historical data from Jani et al (2007)[8] (A) and from Russo et al (2020)[21] (B). o/e LHR, observed to expected lung-to-head ratio.



Fetuses that underwent FETO therapy

A total of 20 fetuses underwent FETO therapy in our cohort, of which 12 had left-sided CDH and 8 had right-sided CDH. The median duration of tracheal occlusion was 14 [10-23] days. The o/e LHR measurements before fetal surgery were 23% [20-28%] in left-sided CDH and 28% [26-37%] in right-sided CDH. Pulmonary hypertension was diagnosed in 15 (75%) infants and the remaining 5 infants died before evaluation. The survival rate was 50% (6/12) in left-sided CDH and 25% (2/8) in right-sided CDH.

Prenatal imaging markers and survival

We performed logistic regression analyses to evaluate the associations between o/e LHR, side of the defect, and FETO therapy against the outcome of survival including our complete cohort. Table 2 depicts the outcomes of the univariate logistic regression models, which showed that o/e LHR only had a significant association with survival in

Table 2 Results for univariate logistic regression for the odds of survival

		All data			Left-sided CDH			Right-sided CDH			No FETO			FETO		
		(n=53)			(n=39)			(n=14)			(n=33)			(n=20)		
		(survival=23)			(survival=19)			(survival=4)			(survival=15)			(survival=8)		
		OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
o/e LHR (%)		1.07	1.01-1.15	0.314	1.11	1.03-1.23	0.017	1.04	0.96-1.15	0.343	1.20	1.07-1.41	0.008	0.98	0.85-1.09	0.675
CDH side	Left (ref.)	-	-	-		NA			NA		-	-	-	-	-	-
	Right	0.42	0.10-1.50	0.199							0.54	0.07-3.26	0.514	0.33	0.04-2.17	0.272
FETO	No (ref.)	-	-	-	-	-	-	-	-	-		NA			NA	
	Yes	0.80	0.25-2.46	0.698	1.08	0.27-4.28	0.915	0.67	0.06-7.55	0.733						

CDH: congenital diaphragmatic hernia; CI: confidence interval; FETO: fetoscopic endoluminal tracheal occlusion; o/e LHR: observed to expected lung-to-head ratio; OR: odds ratio.

infants that received expectant prenatal management and in infants with left-sided CDH. The outcomes of the best fitting multivariable logistic regression model are depicted in Table 3. This final model includes the interaction term between o/e LHR and FETO (Table 3) to account for the interaction between these variables. According to this model, o/e LHR at baseline was positively associated with the odds of survival to discharge in cases that were expectantly managed during pregnancy. Conversely, this association was not present in infants who underwent FETO therapy (OR 1.01, 95% CI 0.88-1.15, *p*=0.87; Table 3). A positive association between FETO and the odds of survival was observed in infants with o/e LHR up to 25% (Table 3). Although not significant, infants with right-sided CDH had lower odds of survival throughout all analyses (Table 2 and 3).

Table 3 Results for multivariable logistic regression for the odds of survival

		All data		
		(n=53)		
		(survival=23)		
		OR	**95% CI**	***p***
o/e LHR (%)	**Without FETO**	1.20	1.07-1.42	0.009
	With FETO	1.01	0.88-1.15	0.865
CDH side	**Left (ref.)**	-	-	-
	Right	0.29	0.04-1.44	0.154
FETO	**No (ref.)**	-	-	-
	at o/e LHR = 25%	7.29	1.25-60.09	0.04
	at o/e LHR = 35%	1.28	0.19-7.99	0.791
	at o/e LHR = 45%	0.22	0.007-5.03	0.354
	at o/e LHR = 50%	0.09	0.001-4.64	0.246

This model includes the interaction term between o/e LHR and FETO therapy.
CDH: congenital diaphragmatic hernia; CI: confidence interval; FETO: fetoscopic endoluminal tracheal occlusion; o/e LHR: observed to expected lung-to-head ratio; OR: odds ratio.

DISCUSSION

Main findings

Our data from over 50 infants with CDH born at or before 32 weeks of gestation suggest that prematurity-related morbidity mainly influences mortality in infants with left-sided CDH and o/e LHR below 35%. Adding to the clinical use of prenatal ultrasound markers, the o/e LHR and stomach position are also associated with the probability of survival to discharge in very preterm born infants with left-sided CDH that are expectantly managed during pregnancy.[8,21]

Interpretation

We observed a slightly higher overall survival rate in CDH infants born at or before 32.0 weeks of gestation than earlier reported: 43% versus 35-38%.[4,25] An explanation for this might be that we, in contrast to earlier series, excluded infants with major chromosomal and structural anomalies. Also, improvements in clinical care over the last 20 years, including the introduction of FETO for severe cases, and the high volume in the participating centres, may have contributed to the higher survival rates.[4]

In our cohort, the survival rates for preterm born infants with left-sided CDH and a lesser degree of lung hypoplasia (o/e LHR ≥36%) seemed not to differ from what was observed in the algorithm of Jani *et al*.[8] Therefore, we speculate that prematurity-related morbidity might be a less important contributor to mortality in this selected group than the underlying pulmonary hypoplasia. It should be emphasised that the algorithm of Jani *et al* consists of historical data potentially underestimating current survival rates, but as similar survival rates were found in more recent studies, we do not expect a significant underestimation of differences between our cohort and this historical cohort. Furthermore, the survival rate in the group with left-sided CDH and o/e LHR of 35% or less was comparable to what is reported for infants with severe hypoplasia (o/e LHR <25%) that are born at a later gestational age.[8] The effect of very preterm birth on survival therefore seems to be most pronounced in the group with severe left-sided CDH. We speculate that one of the explanations for this could be the fact that ECMO therapy is less likely to be offered to infants born preterm or with a birth weight below 1.8 kg.[26] Yet, the benefit of ECMO therapy in CDH is still controversial and, in fact, a considerable variability in its use in term CDH infants is present between the centres included in the current study.[27]

Prenatal grading of stomach position has been shown to correlate with respiratory outcomes and survival in term left-sided CDH infants.[14,15,28] Our results indicate that, also in very preterm born infants with left-sided CDH, the survival rates are different based on stomach position grade, with lower survival rates for higher grades. This is consistent with the predicted outcome by o/e LHR, as a higher stomach grade was associated with a lower o/e LHR. On the other hand, stomach position grade is generally considered a proxy of liver position, but we could not confirm a statistically significant survival advantage in infants with intra-abdominal liver position.[29] This might be a consequence of our limited sample size and the fact that a standardised definition for the assessment of liver herniation is lacking. For this reason, and because of the limited number of cases with MRI investigations, we documented liver position as a dichotomous ultrasound-based variable (yes/no) rather than a continuous MRI-based

variable, which potentially allows for better evaluation of the extent of liver herniation.[30-33]

The association between side of the diaphragmatic defect and survival to discharge has been the subject of debate with some studies indicating higher survival rates in left-sided CDH and others in right-sided CDH.[34,35] In our series, we observed that in this group of very preterm born infants, a right-sided defect resulted in a lower odds of survival than a left-sided defect. Although this effect was consistent in all analyses, it did not reach statistical significance, probably because of the limited number of right-sided CDH cases in our cohort.

FETO therapy has recently been shown beneficial in terms of survival to discharge in infants with severe CDH, but the main limitation of fetal surgery remains the increased rate of preterm birth.[6,21,36] In our study, albeit a small observational retrospective cohort study, we observed apparent higher survival rates in infants that had been treated with FETO therapy, despite very preterm birth and only for left-sided cases.[6] Although these results are in line with recent studies, our observations should be interpreted with caution as our groups are very small.

As FETO therapy increases the chance of survival, the association between baseline o/e LHR (i.e. before fetal surgery) and survival to discharge is expected to be less strong in infants that underwent FETO.[37] In our data, we indeed only observed an association between baseline o/e LHR and survival in infants that had expectant management during pregnancy. Whether the o/e LHR after FETO therapy is associated with survival in very preterm born infants, requires further research.

Strengths and limitations

To the best of our knowledge, this is the first study evaluating the association between various prenatal predictive imaging markers and survival in very preterm born infants with CDH. Albeit data were collected in seven large international referral centres, the rareness of the combination of very preterm birth and CDH inherently results in a limited sample size. We were therefore not able to include additional factors in our predictive models or to evaluate other neonatal outcomes as we wanted to avoid type-I-errors. Also, the number of patients was not sufficient to determine whether alternative cut-offs for severe, moderate, or mild lung hypoplasia would be more accurate for this early gestational age. We do believe that our population is a valid reflection of the overall population of very preterm born CDH infants. Ideally, our results should be evaluated in a larger sample size but reaching a sufficient large sample size in a population managed in a standardised manner will be challenging.

CONCLUSION

The detrimental effects of prematurity-related morbidity are most pronounced in infants with left-sided CDH and expected severe pulmonary hypoplasia. Other than that, currently used prenatal imaging parameters are associated with postnatal survival in very preterm born infants with CDH, although solely in infants that did not receive FETO therapy. Our data provide relevant insights for counselling of parents that face imminent preterm delivery.

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Supplementary Table 1 Odds ratios for mortality given risk factors for preterm birth

	Left-sided CDH (n=27)	Right-sided CDH (n=6)
Amniocentesis	0.83 [0.18-3.88]	NA [a]
Pre-existing maternal disease	0.88 [0.19-4.00]	4.00 [0.10-156.50]
Intra-uterine infection with clinical signs	2.2 [0.33-14.73]	NA [b]
Polyhydramnios	0.47 [0.10-2.29]	0.25 [0.01-9.78]
Preterm premature rupture of the membranes	0.95 [0.20-4.54]	0.08 [0.002- 3.87]

Data are provided as odds ratio [95% confidence interval]. CDH: congenital diaphragmatic hernia.

[a] Odds ratio could not be calculated as 5 out of 6 cases underwent amniocentesis and data was missing in 1 case.

[b] Odds ratio could not be calculated as intra-uterine infection with clinical signs was not present in any case.

PART II

| At birth |

4 | Implementation of delayed cord clamping for 3 minutes during term caesarean sections does not influence maternal blood loss

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ABSTRACT

Background: To assess maternal safety outcomes after a local protocol adjustment to change the interval of cord clamping to 3 minutes after term caesarean section.

Design, Setting and Patients: A retrospective cohort study in a tertiary referral hospital (Erasmus MC, Rotterdam). We included pregnant women who gave birth at term after caesarean section. A cohort (Nov 2016-Oct 2017) prior to the protocol implementation was compared to a cohort after its implementation (Nov 2017-Nov 2018). The study population covered 789 women (n=376 pre-cohort; n=413 post-cohort).

Interventions: Implementation of a local protocol changing the interval of cord clamping to 3 minutes in all term births.

Main outcome measures: Primary outcomes were the estimated maternal blood loss and the occurrence of postpartum haemorrhage (blood loss >1000 ml). Secondary outcomes included both maternal as well as neonatal outcomes.

Results: Estimated maternal blood loss was not significantly different between the pre-cohort and post-cohort (400 ml [300-600] vs 400 ml [300-600], p=0.52). The incidence of postpartum haemorrhage (26 (6.9%) vs 35 (8.5%), OR 1.24, 95% CI 0.73-2.11) and maternal blood transfusion (9 (2%) vs 13 (3%), OR 1.33, 95% CI 0.56-3.14) were not different. Haemoglobin change was significantly higher in the post-cohort (-0.8 mmol/l [-1.3 to -0.5] vs -0.9 mmol/l [-1.4 to -0.6], p=0.01). In the post-cohort, neonatal haematocrit levels were higher (51 vs 55%, p=0.004) and need for phototherapy was increased (OR 1.95, 95% CI 0.99-3.84).

Conclusion: Implementation of delayed cord clamping for 3 minutes in term caesarean sections was not associated with increased maternal bleeding complications.

INTRODUCTION

Severe postpartum haemorrhage (PPH) is one of the most important contributors to maternal mortality, particularly in low resource countries.[1,2] To reduce maternal blood loss, active management of the third stage of labour has been recommended by the World Health Organization (WHO) since 2007, although it was already performed since the 1960s.[2-4] Active management involves three components: (i) prophylactic administration of uterotonic drugs (oxytocin), (ii) controlled cord traction to support placental delivery, and (iii) massage of uterine fundus after placental delivery.[2,5] However, a critical review of this guideline showed that the benefit of this approach was completely attributed to the administration of oxytocin.[1,5-7] On the other hand, to minimise potential neonatal exposure to oxytocin, immediate cord clamping was incorporated into routine clinical practice.[3]

In term infants, the placenta holds up to one-third of the total blood volume and immediate cord clamping would thus withhold this from the neonatal circulation.[8] In contrast, delayed cord clamping optimises placental transfusion and thus results in a higher neonatal blood volume.[1,8,9] Placental transfusion follows a stepwise curve and is completed in two phases: (i) up to 30% of the blood volume is transferred in the first minute after birth, and (ii) the remaining 70% is transferred in the subsequent 2 minutes.[9] Hence performing delayed cord clamping for at least 3 minutes after birth should be considered in each healthy neonate.[10,11] Additionally, immediate cord clamping appears to have a negative effect on cardiovascular adaptations occurring at birth that are better supported when the infant is still connected to the placenta.[12,13] Although healthy term neonates usually experience an uneventful neonatal transition, delayed cord clamping has been shown to improve iron reserves far beyond the first months after birth, and decrease the likelihood of developing anaemia.[10,13-17]

In elective caesarean sections the risk of maternal blood loss is estimated higher, due to the uterine incision and the lack of contractions. Therefore, clinicians have a tendency of clamping the cord shortly after delivery. On the other hand, a recent cohort study demonstrated that immediate cord clamping during a caesarean section was associated with increased neonatal iron deficiency anaemia at 12 and 58 months.[18] Hence, optimising placental transfusion by delaying cord clamping until after 3 minutes would be of particular interest in this population. Based on the above-mentioned recommendations, we have recently implemented delayed cord clamping for 3 minutes as routine practice for all term births. The aim of this study was to audit maternal safety outcomes in caesarean deliveries after this protocol adjustment.

METHODS

This is a single-centre retrospective cohort study performed at Erasmus MC, University Medical Centre (Rotterdam, The Netherlands) comparing two cohorts, before and after a protocol adjustment in November 2017. For both cohorts the study population consisted of all consecutive caesarean sections performed at ≥37 weeks' gestation over a 1-year period. The control group (pre-cohort) consisted of cases between Nov 2016-Oct 2017 and the cohort after the protocol adjustment (post-cohort) consisted of cases between Nov 2017-Nov 2018. The research protocol was approved by the local medical ethical committee (METC 2019-0530) and informed consent was waived due to the retrospective study design.

The protocol adjustment involved implementing delayed cord clamping for all term births for at least 3 minutes after complete birth of the infant. For all caesarean sections, the room temperature in the operation theatre was increased to 23°C. After delivery, the infant was dried and positioned on the maternal chest close to the mother's face. Breathing was encouraged by tactile stimulation and the umbilical cord was protected from kinking or compression. The breathing rate and neonatal heart rate were evaluated after 30 seconds and 1 minute by palpating the cord; when it was deemed appropriate and heart rate was approximately above 60 bpm the procedure was continued (Figure 1). The maternal blood loss was monitored continuously and, if necessary, haemostatic clamps were placed at the uterine incision. In case of excessive blood loss or concerns about the neonatal transition, the procedure was abandoned earlier and the infant was transferred to a resuscitation table for further support. If no exact time of cord clamping was mentioned in the post-cohort patient's history, we concluded that protocol had been followed and that delayed cord clamping of 3 minutes was performed. Oxytocin was administrated after umbilical cord clamping had been performed. The preferred method of placental delivery was spontaneous in both cohorts. All interventions were performed under direct supervision of a consultant in Obstetrics and Gynaecology.

Predefined exclusion criteria for delayed cord clamping consisted of an emergency caesarean section (delivery warranted <10 minutes), maternal general anaesthesia, monochorionic twin pregnancies, higher order multiple pregnancies, placental abnormalities (anterior placenta praevia, invasive placentation), congenital diaphragmatic hernia, and severe cardiac anomalies. We excluded non-eligible cases from further analysis.

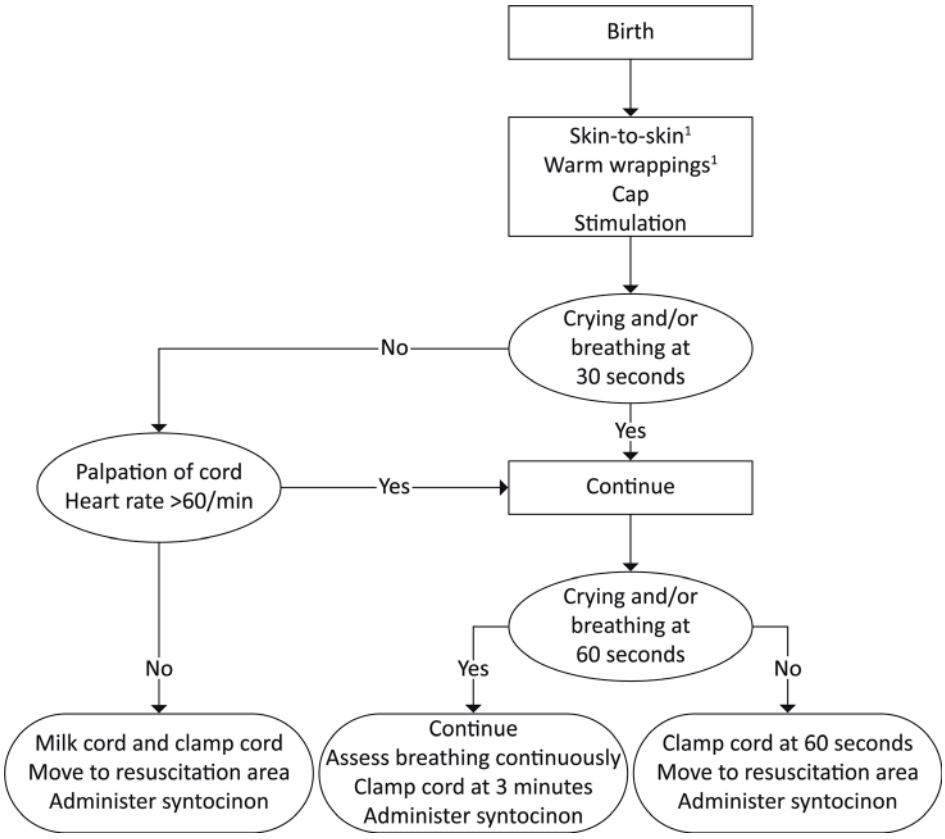

Figure 1 Flowchart of delayed cord clamping protocol at Erasmus MC, The Netherlands.
[1] During caesarean section: first dry, then stimulate. After cord clamping: skin-to-skin with warm wrappings or move to resuscitation area.

The primary outcomes were the estimated maternal blood loss and the occurrence of PPH (blood loss >1000 ml).[19] Maternal blood loss was estimated by the obstetrician using the volume that was in the suction device and on the surgical swabs. Secondary outcomes included both maternal outcomes as well as neonatal outcomes. Maternal secondary outcomes consisted of haemoglobin change before and after caesarean section and the rate of blood transfusions. Neonatal secondary outcomes consisted of infant temperature at admission, moderate hypothermia (temperature <36°C), haematocrit level in the first 24 hours after birth, neonatal intensive care unit admittance, and need for phototherapy in case of icterus neonatorum (confirmed by serum bilirubin sampling). Additionally, baseline characteristics of the neonate were evaluated such as birth weight, Apgar scores at 1 and 5 minutes, and umbilical artery pH. In both groups, an umbilical artery sample was obtained after the umbilical cord had been clamped.

Statistical analyses were performed using the computing environment R [R Core Team (2020), Vienna, Austria, v4.0.2]. Normality was assessed using QQ-plots and density distributions combined with the Shapiro-Wilk test. Continuous data are presented as mean ± standard deviation or median [interquartile range], depending on whether the data were normally distributed. Categorical data are presented as absolute numbers and percentages. Statistical tests for continuous data were the Mann-Whitney U test (non-parametric) and the Student *t* test (parametric). Categorical variables were analysed with a chi-squared test. Results are reported as odds ratio (OR) and 95% confidence interval (95% CI). We analysed the effect of delayed cord clamping on maternal blood loss in the intention-to-treat and per protocol population. The intention-to-treat population is defined as all patients that were included in a particular group (pre-cohort vs post-cohort), independent of protocol adherence. The per protocol population was defined as all patients who received the protocol they were assigned to (immediate cord clamping vs delayed cord clamping at 3 minutes).

RESULTS

In the first cohort 659 caesarean sections were performed; 283 cases were excluded based on the predefined criteria, leaving 376 cases in the pre-cohort for further analysis. In the second cohort 699 caesarean sections were performed; 286 cases were excluded, leaving 413 cases in the post-cohort for further analysis. Table 1 presents the descriptive data of the mothers and neonates. Both groups were not different with regard to demographics and other clinical characteristics, except for umbilical artery blood gas analysis: pH (7.30 [7.26-7.32] vs 7.28 [7.23-7.32], $p<0.001$) and base excess (-2 mmol/l [-3 to 0] vs -3 mmol/l [-5 to -1], $p<0.001$) were significantly lower in the post-cohort.

In the post-cohort, the umbilical cord was clamped at 3 minutes in 53% (218/413) of the infants, at 30-170 seconds in 14% (59/413) of the infants, and immediately (<10 seconds) in 15% (63/413) of the infants. In 18% (73/413) of the infants, timing of cord clamping was not mentioned and we, thus, concluded that protocol was followed. Per protocol populations therefore consisted of 376 subjects for the immediate cord clamping group and 291 subjects for the delayed cord clamping group (3 minutes).

Table 1 Baseline characteristics

	Pre-cohort		Post-cohort	
	n	(n=376)	n	(n=413)
Maternal age (years)	376	32 ± 5	413	32 ± 5
Nullipara	376	150 (40)	413	162 (39)
Elective caesarean section	376	235 (63)	413	264 (64)
Gestational age at birth (weeks)	376	39.0 [38.3-39.4]	413	39.0 [38.1-39.3]
Umbilical artery pH	368	7.30 [7.26-7.32]	399	7.28 [7.23-7.32]
Umbilical artery pCO2 (kPa)	363	7.20 [6.60-7.90]	399	7.20 [6.55-8.00]
Umbilical artery base excess (mmol/L)	362	-2 [-3 to 0]	395	-3 [-5 to -1]
Birthweight (g)	375	3327 ± 521	413	3349 ± 554
Apgar 1'	354	9 [8-9]	397	9 [8-9]
Apgar 5'	359	10 [9-10]	398	10 [9-10]

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

Table 2 Primary outcomes

	Pre-cohort		Post-cohort		
	n	(n=376)	n	(n=413)	
Maternal blood loss (mL)	375	400 [300-600]	413	400 [300-600]	*p*=0.52
Maternal blood loss >1000 mL	375	26 (6.9)	413	35 (8.5)	OR 1.24 (95% CI 0.73-2.11)

Data are expressed as median [interquartile range] or n (%).

Table 2 shows the results of the primary outcomes in the intention-to-treat analysis. The median maternal blood loss did not significantly differ between pre-cohort and post-cohort (400 ml [300-600] vs 400 ml [300-600], *p*=0.52). In addition, there was no difference in the incidence of PPH: 26 mothers in the pre-cohort and 35 mothers in the post-cohort (OR 1.24, 95% CI 0.73-2.11). Per protocol analysis again demonstrated no difference in median maternal blood loss in immediate cord clamping compared to delayed cord clamping (400 ml [300-600] vs 400 ml [300-500], *p*=0.60) and no difference in the incidence of PPH (OR 0.78, 95% CI 0.41-1.48). Secondary maternal outcomes are presented in Table 3. Haemoglobin change was significantly different in the pre-cohort and post-cohort (-0.8 mmol/l [-1.3 to -0.5] vs -0.9 mmol/l [-1.4 to -0.6], *p*=0.01). The rate of maternal blood transfusions was not significantly different (OR 1.33, 95% CI 0.56-3.14).

Table 3 Secondary outcomes

	Pre-cohort		Post-cohort		
	n	(n=376)	n	(n=413)	
Maternal haemoglobin before delivery (mmol/L)	373	7.4 [6.9-7.9]	407	7.4 [6.9-7.9]	*p*=0.9
Maternal haemoglobin after delivery (mmol/L)	366	6.4 [5.9-6.9]	408	6.4 [5.8-6.9]	*p*=0.1
Maternal haemoglobin difference (mmol/L)	365	-0.8 [-1.3 to -0.5]	402	-0.9 [-1.4 to -0.6]	*p*=0.01
Maternal blood transfusion	376	9 (2)	413	13 (3)	OR 1.33 (95% CI 0.56-3.14)
Neonatal intensive care unit admittance	376	79 (21)	413	79 (19)	OR 0.89 (95% CI 0.63-1.26)
Temperature of neonate (°C)	116	37.1 [36.7-37.3]	412	36.7 [36.3-37.0]	*p*<0.001
Haematocrit level of neonate (%)	69	51 ± 8	63	55 ± 8	*p*=0.004
Phototherapy	376	13 (3)	413	27 (7)	OR 1.95 (95% CI 0.99-3.84)

Data are expressed as median [interquartile range] or n (%).

Neonatal outcomes are depicted in Table 3. Infant temperature at admission to the ward was lower in the post-cohort. The number of infants with moderate hypothermia was higher in the post-cohort (2/116 (2%) vs 29/412 (7%), OR 4.32, 95% CI 1.01-18.36). Neonatal haematocrit levels were significantly higher in the post-cohort, and the need for phototherapy was higher in the post-cohort (OR 1.95, 95% CI 0.99-3.84). The majority of infants receiving phototherapy had at least one serum bilirubin value that was equal to or higher than the intervention threshold for that specific infant: 85% (11/13) in the pre-cohort and 96% (26/27) in the post-cohort. The highest measured serum bilirubin values in infants receiving phototherapy were similar in both groups (286 µmol/l [230-323] vs 297 µmol/l [263-320], *p*=0.36).

There was no difference in rates of admission to the neonatal intensive care unit. In our tertiary care centre population, 41% of all neonatal intensive care unit admissions were because of congenital malformations.

DISCUSSION

Our study adds information on the safety of delaying cord clamping until placental-to-neonatal transfusion is completed during term caesarean sections. In this study we did not observe differences in maternal blood loss and the incidence of PPH after implementing delayed cord clamping for 3 minutes as a routine practice. In addition, neonatal haematocrit levels in our trial were significantly higher after the imple-

mentation of delayed cord clamping, highlighting the importance of optimising the placental-to-neonatal transfusion.

Our observations are in line with earlier trials that have already demonstrated that delayed cord clamping beyond 60 seconds during a vaginal delivery was not associated with increased maternal morbidity.[4,20] Nonetheless, the risk for maternal bleeding complications is estimated higher in caesarean section because of the lack of adequate uterine contractions. Hence, this resulted in a relative scepticism for implementing delayed cord clamping during a caesarean section. An important consideration is the delayed administration of oxytocin to avoid any influence on the placental-to-neonatal transfusion. However, a recent study showed that oxytocin could be administered prior to cord clamping without affecting the placental-to-neonatal transfusion.[21] Previous studies evaluating delayed cord clamping in caesarean sections, though shorter durations (range 30-120 seconds), also did not report an increase in estimated maternal blood loss.[20,22-24] In our study, the incidence of PPH remained stable after implementation of the protocol (6.9% vs 8.5%) and reassuringly this is comparable to what is reported in a recent small randomised controlled trial comparing delayed cord clamping to immediate cord clamping in term caesarean delivery.[23] Although we observed a significantly higher decrease in maternal haemoglobin after caesarean section, the clinical relevance of a difference of 0.1 mmol/l is certainly debatable. In particular as this difference did not translate into a higher incidence of maternal blood transfusions.

Neonates born through caesarean section are at higher risk for developing neonatal anaemia since the placental-to-neonatal transfusion might be compromised because of a tendency to perform immediate cord clamping.[1,25] In our trial, we showed a benefit of delayed cord clamping on neonatal haematocrit levels, yet the optimal interval till clamping the cord is not firmly established. We based our protocol on a series of papers published more than 50 years ago, but others have observed a considerable individual variability in the time to complete placental transfusion (ranging between 2 to 5 minutes).[9,26] Likewise, the impact of uterine contractions and breathing is not well-established.[27] This is particularly important given that the potential side-effect of the additional blood volume is neonatal hyperbilirubinemia and the need for phototherapy, due to breakdown of red blood cells. The need for phototherapy in our study was higher in neonates after delayed cord clamping, as was also demonstrated in earlier trials.[1,8,28]

Neonatal temperature management in the delivery room is of high importance, since hypothermia is associated with a higher risk of hypoglycaemia and respiratory

distress.[29] Hypothetically, the umbilical blood is heated to the maternal core temperature after passage through the placenta, providing an internal heat source and, thus, potentially preventing hypothermia in delayed cord clamping. We could not confirm this hypothesis, on the contrary, we observed a significantly lower median infant temperature at admission to the ward after performing delayed cord clamping. In addition, we observed an increased incidence of moderate hypothermia, but the large number of missing data in the pre-cohort makes it difficult to draw firm conclusions, which is reflected by the large confidence interval. Nonetheless, our findings emphasise the importance of adequate measures to ensure optimal temperature management, especially during caesarean section. In our local protocol we have implemented additional measures such as sterile hats for the neonate and increased focus on drying the infant thoroughly.

We noticed a lower cord blood pH in the post-cohort. This was recently also reported in a prospective study evaluating the effect of delayed cord clamping on cord blood analysis in uncomplicated births. Delayed cord clamping at caesarean section resulted in a mixed respiratory and metabolic acidosis with increased pCO_2 and lactate, in combination with a reduction in base excess.[30-32] In our data, we confirmed the moderate decrease in base excess, but pCO_2 values were not different. Regardless, this did not translate in increased adverse neonatal outcomes or neonatal intensive care unit admission rates. However, the incidence for the latter was in both groups remarkably higher than in previous trials (20% vs 8%).[24] This is a reflection of the patient population at our institution as a tertiary referral centre with a high incidence of congenital neonatal pathology.

The current study provides reassuring evidence about maternal safety when performing delayed cord clamping for a prolonged period in an attempt to improve placental-to-neonatal transfusion and thus neonatal iron reserves. This is important for future projects that aim to implement this in low resource settings, as the access to medications and equipment to control maternal bleeding is generally limited.

A strength of this study is that it evaluates a protocol implementation in a heterogenic group of patients that is a relevant representation of the general population for many centres. Furthermore, this study is the largest series so far evaluating the risks of delayed cord clamping during term caesarean sections and with a prolonged period of 3 minutes there was no higher risk of maternal bleeding complications. Limitations of adopting our findings into clinical practice are that this is a single-centre trial in a high-income country in which we have easy access to drugs and equipment needed to control both maternal bleeding and the neonatal temperature. Estimating the amount

of maternal blood loss was at the clinician's discretion, thereby introducing potential researcher bias. However, at the time of surgery, the clinicians were unaware of this study and, thus, the impact of this seems limited. Furthermore, we included objective variables evaluating the maternal blood loss such as maternal blood transfusions and haemoglobin differences. Protocol adherence in the post-cohort was not optimal with only 71% of the infants receiving delayed cord clamping for 3 minutes. Protocol adherence was similar in the first 6 months and the last 6 months of the post-cohort (69 vs 72%). Reasons for early cord clamping were among others increased maternal bleeding and need for neonatal support. The retrospective design also introduces the risk of bias which is important to consider when interpreting the results, such as the incidence of moderate hypothermia. Around the same time of introducing delayed cord clamping, our hospital also altered its registration system for neonatal parameters. This new system resulted in improved documentation, explaining the difference with the cohort after protocol adjustment.

CONCLUSIONS

Delayed cord clamping for 3 minutes during term caesarean sections appeared not to result in increased maternal bleeding complications. This study adds to the growing body of evidence assessing maternal safety when optimising placental transfusion.

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5 | Physiological-based cord clamping versus immediate cord clamping for infants born with a congenital diaphragmatic hernia (PinC): study protocol for a multicentre, randomised controlled trial

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ABSTRACT

Introduction: Pulmonary hypertension is a major determinant of postnatal survival in infants with a congenital diaphragmatic hernia (CDH). The current care during the perinatal stabilisation period in these infants might contribute to the development of pulmonary hypertension after birth – in particular umbilical cord clamping before lung aeration. An ovine model of diaphragmatic hernia demonstrated that cord clamping after lung aeration, called physiological-based cord clamping (PBCC), avoided the initial high pressures in the lung vasculature while maintaining adequate blood flow, thereby avoiding vascular remodelling and aggravation of pulmonary hypertension. We aim to investigate if the implementation of PBCC in the perinatal stabilisation period of infants born with a CDH could reduce the incidence of pulmonary hypertension in the first 24 hours after birth.

Methods and analysis: We will perform a multicentre, randomised controlled trial in infants with an isolated left-sided CDH, born at ≥35.0 weeks. Before birth, infants will be randomised to either PBCC or immediate cord clamping, stratified by treatment centre and severity of pulmonary hypoplasia on antenatal ultrasound. PBCC will be performed using a purpose-built resuscitation trolley. Cord clamping will be performed when the infant is considered respiratory stable, defined as a heart rate >100 bpm, preductal oxygen saturation >85%, while using a fraction of inspired oxygen of <0.5. The primary outcome is pulmonary hypertension diagnosed in the first 24 hours after birth, based on clinical and echocardiographic parameters. Secondary outcomes include neonatal as well as maternal outcomes.

Ethics and dissemination: Central ethical approval was obtained from the Medical Ethical Committee of the Erasmus MC, Rotterdam, The Netherlands (METC 2019-0414). Local ethical approval will be obtained by submitting the protocol to the regulatory bodies and local institutional review boards.

INTRODUCTION

A congenital diaphragmatic hernia (CDH) is a birth defect characterised by incomplete closure of the diaphragm. Abdominal organs herniate into the fetal thorax and interfere with lung development, thereby contributing to the development of pulmonary hypoplasia.[1-8] Pulmonary hypoplasia translates in delayed lung aeration after birth, thereby requiring prompt resuscitation and respiratory support. In anticipation of this requirement, the umbilical cord is usually clamped immediately after birth so that the infant can be transferred to a resuscitation table. Despite extensive respiratory support, infants with a CDH face significant mortality (around 30% in most series) and long-term morbidity, with many survivors suffering from chronic respiratory problems and pulmonary hypertension.[9-12] The aetiology of pulmonary hypertension in infants with a CDH is multifactorial. Abnormal structural development of the vasculature, altered vasoreactivity, and progressive vascular remodelling are considered important factors in developing and maintaining high perfusion pressures in the lungs.[13-15] Postnatal left ventricular systolic dysfunction correlates with outcomes in infants with a CDH and also contributes to the development of pulmonary hypertension.[16,17] Pulmonary hypertension can develop in the first hours after birth and can persist for weeks to even months. The presence of severe pulmonary hypertension at 1 month of life is associated with a 56% mortality rate prior to discharge.[18] Current treatment options for pulmonary hypertension are limited and mainly consist of pulmonary vasodilator drugs with varying responses and the use of extracorporeal membrane oxygenation.[19]

Currently, immediate cord clamping is performed in almost all infants born with a CDH. Before cord clamping, oxygenated blood in the umbilical veins shunts to the left atrium via the ductus venosus and foramen ovale, thereby guaranteeing venous return to the left ventricle of the heart.[20,21] Thus, clamping the cord separates the infant from both its oxygen source as well as the blood flow required to maintain left ventricular preload.[20,21] In addition, left ventricular afterload increases when the low-resistance circulation of the placenta is removed.[20,21] As a result, cardiac output decreases. In term neonates with normal lung development, lung aeration causes the pulmonary vascular resistance to decrease and the pulmonary blood flow to increase, allowing the lungs to take over from the placenta in providing gas exchange (oxygenation) and maintaining cardiac output.[20,21]

In contrast, most infants born with a CDH are faced with a complicated transition from the fetal to the neonatal phenotype. Due to the abnormally developed pulmonary vasculature and hypoplastic lungs, lung aeration is delayed and, thus, the pulmonary vascular resistance does not decrease sufficiently to accommodate the entire output of the right

ventricle.[21-23] Pulmonary vascular pressures then increase and potentially result in a reactive vasospasm triggering vascular remodelling, perpetuated by ongoing hypoxic pulmonary vasoconstriction.[23] When lung aeration is established prior to clamping the cord, called physiological-based cord clamping (PBCC), the lungs will already have taken over the placental function before the cord is clamped, thereby avoiding the hypoxia and high pulmonary arterial pressures that can occur after immediate cord clamping (Figure 1). Recently, in an ovine model of a diaphragmatic hernia, we have confirmed that PBCC resulted in significantly lower pulmonary arterial pressures while maintaining higher pulmonary blood flows up to 20 and 120 minutes after birth, respectively.[23] PBCC, thus, has the potential to influence the functionality of the pulmonary vessels.

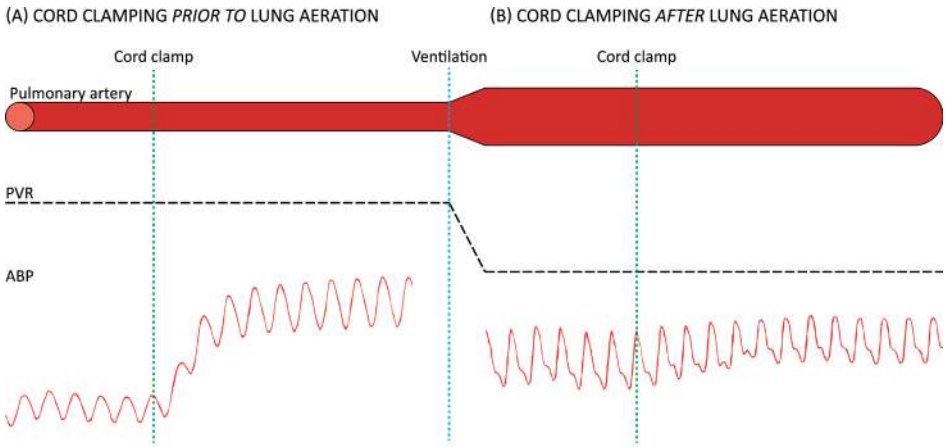

Figure 1 Fetal-to-neonatal transition in congenital diaphragmatic hernia. (A) Clamping the umbilical cord prior to lung aeration has been established and, thus, prior to the pulmonary vascular resistance (PVR) has decreased, increases the arterial blood pressure (ABP, afterload) and decreases the preload to the left ventricle. As a result, the cardiac output decreases. (B) Clamping the umbilical cord after lung aeration has been established and, thus, after the PVR has decreased, will result in a more stable transition. In that case, the left ventricular afterload and preload remain stable.

Two recent feasibility studies described the concept of initiating respiratory support prior to cord clamping in infants with a CDH.[24,25] Both studies confirmed that this approach was feasible and had promising effects on the cardiovascular adaptation in the first hours after birth, although neither studies were powered to detect differences in outcomes.[24,25] Hence, the logical next step is a randomised clinical trial to determine the true benefit of PBCC for infants with a CDH.[26] We hypothesise that implementing a non-invasive intervention (such as PBCC) during the perinatal stabilisation period avoids initial high pulmonary perfusion pressures that initiate a vasoreactive response, thereby reducing the risk of pulmonary hypertension. The primary aim of this study is to investigate if the implementation of PBCC in the stabilisation period of infants

born with a CDH reduces the incidence of pulmonary hypertension in the first 24 hours after birth, a clinically relevant outcome in these infants. The secondary aim of this study is to perform real-time monitoring of physiological parameters, which will improve our understanding of the physiological changes occurring during the perinatal stabilisation period in this population of infants.

METHODS AND ANALYSIS

Study design

The PBCC in CDH (PinC) trial is an international randomised controlled trial, that will be conducted in multiple academical centres in Europe and Australia. Infants will be randomised to either PBCC or immediate cord clamping (Figure 2), whereas ongoing management will be according to a consensus-based postnatal management protocol.[19]

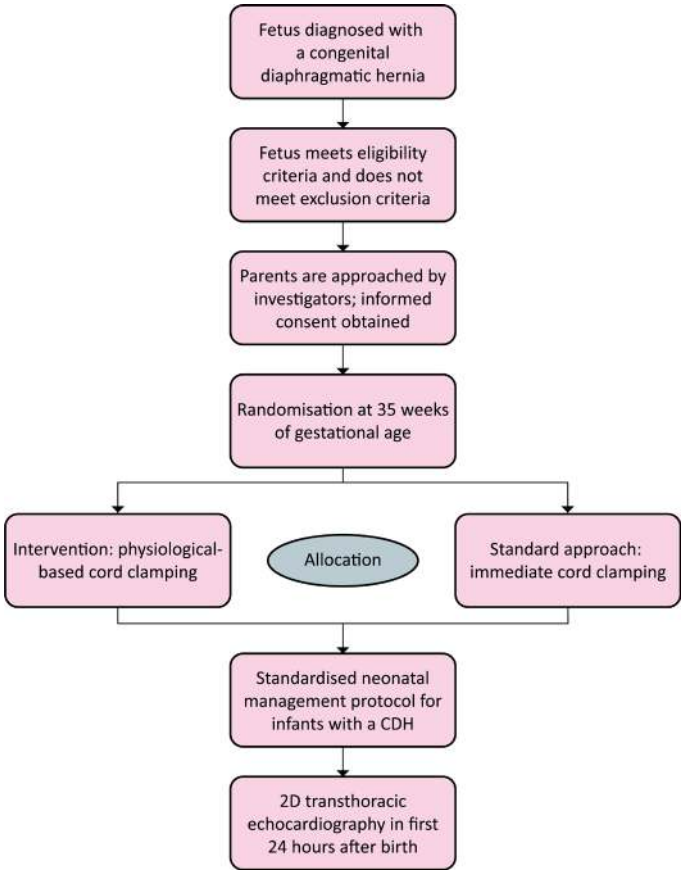

Figure 2 Trial flowchart. The flowchart depicts the steps from the screening of a subject until the evaluation of the primary outcome of the trial. CDH: congenital diaphragmatic hernia.

Patient and public involvement

Patients were not involved in the design of this study.

Patient population

We will include infants diagnosed with an isolated left-sided CDH on prenatal ultrasound with gestational age at delivery ≥35.0 weeks. Exclusion criteria are right-sided and bilateral CDH, antenatal diagnosed major associated structural or genetic abnormalities, high urgency caesarean section (intended interval to delivery <15 min), cases that have been treated during pregnancy with experimental drug therapy aiming to decrease the occurrence of pulmonary hypertension, twin pregnancies in which the infant diagnosed with a CDH is born first, multiple birth >2, and placental abnormalities (anterior placenta praevia, placental abruption).

Randomisation

Participants will be randomised using Castor electronic data capture (EDC), an EDC system that uses a computer-generated randomisation list and, thus, ensures concealment of allocation. Infants will be randomised 1:1 to either PBCC or the current standard approach of immediate cord clamping. Allocation will be stratified by predicted lung size (determined by observed to expected lung-to-head ratio and liver position, graded as mild/moderate/severe lung hypoplasia, measured between 20 and 26 weeks or at the initial visit) and by treatment centre, using variable random permutated block sizes (4-8).[27]

Study procedures

Providing adequate respiratory support immediately after birth while performing PBCC requires a resuscitation table near the mother. To facilitate this approach, several trolleys have been developed and we will preferably use the Concord Birth Trolley (Concord Neonatal B.V., Leiden, The Netherlands). This trolley was purpose-built for PBCC and has shown excellent feasibility in preterm infants.[28] The trolley is fully equipped for stabilisation of infants with a CDH. In all infants, we will use a monitor that records vital parameters during stabilisation. Prior to the start of the study, all caregivers involved in delivery room care will be trained using the Concord.

In PBCC, the Concord will be placed next to the bed of the mother and all equipment will be checked before the second stage of labour has started (Figure 3). The infant will be placed on the platform of the Concord immediately after birth, avoiding any traction or pressure on the cord and avoiding heat loss by radiation heating. The umbilical cord will not be clamped until the infant is considered respiratory stable, which is defined as the presence of a heart rate >100 bpm and preductal oxygen saturation >85%, while

Figure 3 Position of the Concord birth trolley. The Concord birth trolley is positioned at the left side of the mother. The infant is then stabilised while the umbilical cord is still intact. The Concord birth trolley is fully equipped for stabilisation of infants that are born with a congenital diaphragmatic hernia.

using a fraction of inspired oxygen of <0.5. Oxytocin administration will be postponed until after cord clamping if there are no obstetric concerns. To both guarantee an optimal placental-to-fetal transfusion as well as avoid excessive maternal blood loss, the minimum and maximum times of cord clamping are 3 and 10 minutes after birth, respectively.[29] At any time, the attending neonatologist and obstetrician can decide that PBCC should not be performed or be interrupted. In that case, the infant can be placed on the standard resuscitation table for (further) stabilisation. In this trial, physicians cannot be blinded to treatment allocation. However, we believe that the lack of blinding will not lead to deviations from the intended intervention, hence the influence on the primary outcome will be limited. In the immediate cord clamping group, the cord will be clamped immediately after birth. The infant will then be transferred to the standard neonatal resuscitation table. Thermomanagement during stabilisation is an important focus in both groups since hypothermia is a known trigger for pulmonary hypertension. Normal precautions will be taken to prevent heat loss, such as dry towels, caps, and a radiant warmer. After cord clamping, all infants will be managed according to the standardised neonatal management protocol for infants with a CDH, which is a consensus of current clinical guidelines by the CDH EURO consortium.[19] A 2D echocardiography will be performed within the first 24 hours of life to evaluate the presence or absence of pulmonary hypertension.

This trial provides the unique possibility of collecting umbilical cord blood samples from a significant number of infants with a CDH that will have been randomised for two

different stabilisation methods. We speculate that the physiological changes during the stabilisation period could trigger the release of biomarkers, such as free oxygen radicals, iron/hepcidin and metabolomics. Free oxygen radicals stimulate pulmonary vasoconstriction and could thus contribute to the occurrence and therapy-resistance of pulmonary hypertension.[30] These biomolecules also induce lipid peroxidation modifying certain metabolic pathways, such as the endocannabinoid metabolism. Endocannabinoids are an interesting target for further analysis because of their involvement in supporting the fetal-to-neonatal transition.[31] A second promising pathway is iron homeostasis, in particular the regulatory protein hepcidin. Iron-deficiency seems to alter smooth muscle cell activity, influence pulmonary vascular function, and, thus, contribute to the severity of pulmonary hypertension.[32] Hepcidin treatment in rats with pulmonary hypertension resulted in a decrease in right ventricular systolic pressure and mean pulmonary arterial pressure, and with that in a decrease in pulmonary lesions induced by pulmonary hypertension.[33] In this trial, samples will be collected and stored in a Biobank in the Erasmus MC. Cord blood will be analysed to detect relevant biomarkers in the prediction of postnatal outcomes. The above-mentioned biomarkers could eventually be used as early predictors of both short- and long-term outcomes, thereby allowing early interventions and individualised treatments, and specialised package of care.

Table 1 Primary outcome

Pulmonary hypertension is present if at least 2 of the following 4 criteria are present or if the infant requires extracorporeal membrane oxygenation in the first 24 hours after birth:	
1	Right ventricular systolic pressure ≥2/3 systemic systolic pressure [a]
2	Right ventricle dilatation/septal displacement or right ventricular dysfunction ± left ventricular dysfunction [a]
3	Difference between preductal and postductal oxygen saturation >10% [b]
4	Oxygenation index >20 [b]

a On first ultrasound in first 24 hours after birth.
b Highest values measured during first 24 hours after birth.

Primary and secondary outcomes

The primary study outcome is pulmonary hypertension diagnosed in the first 24 hours after birth combining clinical and echocardiographic parameters (Table 1). As the physician assessing the echocardiogram cannot be blinded to the intervention in all centres, we will collect the following echocardiographic parameters to guarantee objective evaluation of the presence or absence of the echocardiographic parameters: right ventricular systolic pressure, right ventricular size, pulmonary artery acceleration time (PAAT), right ventricular ejection time (RVET), PAAT:RVET ratio, intraventricular septum configuration, left ventricular end-systolic eccentric-

ity index, tricuspid regurgitation, peak velocity of tricuspid regurgitation, tricuspid annular plane systolic excursion, transductal shunting direction, interatrial shunting direction, and right ventricular systolic to diastolic duration ratio.[34]

Secondary outcomes that will be reported in the total population:
- Maternal blood loss during delivery, estimated using the volume in the suction device and on the surgical swabs.
- Time interval between birth and start respiratory support.
- Apgar scores.
- Umbilical cord pH.
- Temperature at admission to the intensive care unit.
- Respiratory support during resuscitation.
- Mortality.

Secondary outcomes that will be reported in the total population and in the subgroup of survivors separately:
- Presence of pulmonary hypertension requiring therapy on day 7, 14, 21, 28, and at discharge.
- Treatment for pulmonary hypertension.
- Use of inotropes and fluid therapy.
- Presence of early-onset and late-onset sepsis.
- Surgical characteristics.
- Presence of hyperbilirubinemia requiring therapy.
- Presence of neurological complications.
- Respiratory support during hospitalisation.
- Presence and severity of bronchopulmonary dysplasia.
- Number of days on the intensive care unit.

Postpartum haemorrhage is considered a safety parameter, because PBCC will result in later cord clamping times than are currently used for infants with a CDH.

Data collection

All outcome variables will be collected by local physicians and will be entered in a password protected online database (Castor EDC). Data access will be granted to the principal investigators of all participating centres. On request the collected data will be available.

Informed consent

Informed consent will be obtained before birth and the procedure will be explained to the parents by the investigators during a specific antenatal counselling session, followed by a time of reflection for the parents.

Data and Safety Monitoring

The data and safety monitoring board will conduct two interim statistical analyses on safety during the course of this study, after approximately 25% and 50% of the total required patients have completed their primary outcome. The only stopping condition will be concerns regarding safety outcomes. The safety analysis will include, but will not be restricted to, serious adverse events and the context-specific safety outcomes listed as secondary outcomes (bronchopulmonary dysplasia, sepsis, cerebral complications, need for extracorporeal membrane oxygenation). An annual safety report of all context-specific serious adverse events will be presented to the data and safety monitoring board and approving ethics committee. All other serious adverse events will be reported to the approving ethics committee in accordance with their guidelines.

Sample size estimates

The background incidence of pulmonary hypertension in infants with a CDH can be estimated based on historical cohorts. The largest registry available is the CDH Study Group registry consisting of data from 70 participating centres in 13 countries. A recent review of 3367 patients of this cohort (2007-2014) reports a 69.7% incidence of pulmonary hypertension in the first week after birth (median of 0 days (0-8)).[35] As this is the first human clinical study evaluating PBCC with pulmonary hypertension as primary outcome, we cannot estimate the effect size. Thus, we suggest using a clinically relevant change in incidence of pulmonary hypertension to determine the sample size. We consider that a relative decrease by one-third in the incidence of pulmonary hypertension in the first 24 hours after birth is realistic and is significant enough to influence change in the neonatal management of infants with a CDH. Based on the background incidence of pulmonary hypertension, we calculated that at least 140 infants (70 in each group) are needed to detect a one-third reduction, with 80% power and 0.05 significance level. It will be difficult to estimate the number of cases that will have the umbilical cord clamped earlier than the times within the PBCC protocol. However, based on the results from two small human feasibility studies, it can be expected that we will have good overall adherence to the protocol.

Statistical analyses

The effect of PBCC on the primary outcome (pulmonary hypertension) will be analysed in the intention-to-treat population. The intention-to-treat population is defined as all patients that were randomised to a particular treatment arm, independent of protocol deviations. The effect will be analysed using multivariable logistic regression analysis with pulmonary hypertension as dependent variable and treatment allocation, severity of pulmonary hypoplasia, and treatment centre as independent variables. Per protocol analysis for the primary outcome will be employed as secondary analysis. The per protocol population is defined as all randomised patients who completed the protocol for the arm they were assigned to, had the primary endpoint measured, and had no major protocol violations.

The primary analysis will be a complete case analysis. By protocol, the independent variables in this multivariable analysis will be present in all cases. The dependent outcome could however be missing in the rare event that evaluation has not been performed in the first 24 hours after birth. We will perform a sensitivity analysis by imputing missing values in the primary outcome by using the 'worst case' observed in cases in which the primary outcome was assessed.

If more than 20% of values on a secondary outcome are missing, we will remove that variable from analyses. If no more than 20% of a secondary outcome are missing, we will use multiple imputation to deal with the missing data. Additionally, we will perform a sensitivity analysis by replacing missing values with the 'worst case' observed in patients with available data. For secondary outcomes we will calculate risk ratios or odds ratios with 95% confidence intervals.

All data will be tested for normality using a Shapiro-Wilk test. Normally distributed data will be presented as mean ± standard deviations, not-normally distributed data as medians (interquartile ranges). Statistical significance is set at $p<0.05$, using two-sided tests. Statistical analyses will be performed using the computing environment R (R Core Team (2020), Vienna, Austria).

ETHICS AND DISSEMINATION

Central ethical approval was obtained from the Medical Ethical Committee of the Erasmus MC, Rotterdam, The Netherlands (METC 2019-0414). Local ethical approval was obtained from the ethical committees of the University Hospital of Graz, Austria; the Radboudumc University Medical Centre, Nijmegen, the Netherlands; Monash

Health, Clayton, Australia; University Hospitals Leuven, Belgium. The study is in the final stage of the review process by the ethical committees of the University of Bonn, Germany, and the University Medical Centre Mannheim, Germany. The study will be conducted according to the principles of the Declaration of Helsinki and international rules and regulations on personal data protection. The results of this study will be disseminated via peer-reviewed publications.

Trial status

Currently five university medical centres are enrolling patients. The first patient was included on 11 May 2020, and by 8 March 2022, 24 patients had been included. In 2022, two additional international centres will be added. Final inclusion is expected in 2023. The current article is based on protocol version 1.5 (15 March 2021).

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6 Routine intubation in newborns with congenital diaphragmatic hernia

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INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a rare developmental defect of diaphragm and lungs, resulting in pulmonary hypoplasia and pulmonary hypertension (PH). With improved prenatal diagnostics, lung hypoplasia severity in CDH can be classified more accurately.[1,2] Infants with isolated left-sided CDH, observed to expected lung-to-head ratio (o/e LHR) ≥50%, and intra-abdominal liver position are categorised as "mild lung hypoplasia" because their survival rate exceeds 95%.[1,3] All international guidelines advise routine intubation at birth for neonates with CDH to establish adequate oxygenation and cardiovascular stability.[4-7] However, in mild CDH, this potentially results in overtreatment and disturbance of physiologic perinatal transition.[8] Our aim with this study was to evaluate a spontaneous breathing approach (SBA) in the treatment algorithm of infants with mild CDH.

METHODS

After study approval by the local institutional review board (MEC2019-714) and waived informed consent, we performed a retrospective study in newborns with CDH born at Erasmus University Medical Centre Rotterdam, a national and level 3 referral centre with extracorporeal membrane oxygenation.

Our local protocol is based on the CDH EURO Consortium guidelines. Accordingly we modified our protocol in December 2014, allowing planned SBA in patients with mild CDH born >35 weeks of gestation.[4] We used the o/e LHR measured between 24 and 38 weeks of gestation.[1] Congenital anomalies were defined as anatomic anomalies on prenatal ultrasound or genetic mutations (microarray). We included all patients with mild CDH born between December 2014 and July 2019. The SBA was classified as failed if the infant required intubation any time before elective intubation for surgery. Surgery was planned electively with an experienced CDH operating team.

In our centre, a perinatal treatment plan is made for all patients with CDH in a multidisciplinary team meeting at ~32 weeks of gestation, attended by obstetricians, fetal medicine specialists, neonatologists, paediatric intensivists, and surgeons. The treatment strategies are subsequently discussed with the parents, including an SBA if applicable. Postnatal resuscitation is executed according to the EURO CDH Guidelines.[4] The newborn is positioned on the resuscitation table and a replogle tube (10F catheter) is inserted for continuous stomach decompression. In the case of planned SBA, the infant is supported with oxygen if necessary (Neopuff infant T-

piece resuscitator; Fisher & Paykel Healthcare, Ltd, Auckland, New Zealand), aiming for preductal saturations >85%.[4] Continuous positive airway pressure is allowed. The infant is intubated if insufflation breaths or ventilation are needed because positive pressure ventilation via mask increases the air in the digestive tract, subsequently compressing the lungs, resulting in hypoxia and PH.

Patient characteristics and outcome parameters were described as numbers or percentages for categorical data or median (interquartile range) for continuous data. The Mann-Whitney *U* test was used to compare patients with successful and failed SBA.

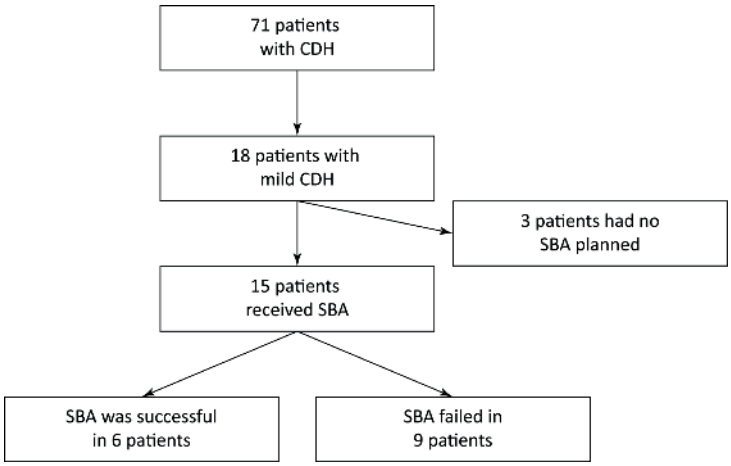

Figure 1 Patient flowchart. Flowchart of patient selection for the case series.
CDH: congenital diaphragmatic hernia; SBA: spontaneous breathing approach.

RESULTS

During the study period, 71 newborns with CDH were treated in our referral centre, and 18 (25%) fulfilled the SBA criteria. However, in 3 patients, SBA was not prenatally planned and, thus, not performed (Figure 1). SBA was successful in 6 of 15 patients (40%); 3 required continuous positive airway pressure for several minutes, and 5 were transferred to the unit with binasal cannulae (Intersurgical, Inc, Syracuse, NY) with 1 to 2 litre flow and 30-40% of inspired oxygen. All were electively intubated for surgery. In total, 9 of 15 patients required intubation after birth (7 at birth and 2 several hours after birth). Only 1 patient (o/e LHR 57%) developed PH and was treated with inhaled nitric oxide for 4 days and oxygen supplement therapy for 28 days. Apart from the anticipated difference in ventilation days and duration of oxygen therapy, there were no clinical differences between patients with successful and failed SBA (Table 1). The overall survival was 100%.

Table 1 Patients with and without successful SBA

	Successful SBA (n=6)	Failed SBA (n=9)	*p*
Male	3 (50)	7 (78)	
Birth weight (kg)	2.78 [2.38-3.22]	3.0 [2.85-3.20]	0.24
Apgar 1'	8 [6-8]	7 [4-8]	0.41
Apgar 5'	8 [8-9]	7 [7-9]	0.18
Gestational age at birth (weeks)	37.8 [37.0-38.5]	38.3 [37.9-38.6]	0.37
o/e LHR (%)	66.0 [49.8-82.3]	55.0 [52.0-64.5]	0.56
Peak ventilator pressure [a] (cmH_2O)	23.5 [21.5-27.0]	23.0 [19.5-25.0]	0.37
VIS score [a]	0 [0-18.8]	4.6 [0-15.5]	0.57
Days on ventilator	1.0 [1.0-2.5]	7.0 [4.0-10.0]	<0.05
Age at surgical repair (days)	3 [2-4]	3 [2-5]	0.90
Defect size			0.89
A	0	2 (22)	-
B	2 (33)	5 (56)	-
C	1 (17)	0	-
D	0	0	-
Missing	3 (50)	2 (22)	-
Patch repair	2 (33)	5 (56)	0.53
Days on ventilator after surgery	1.0 [1.0-2.5]	4.0 [2.0-5.5]	0.05
Total days oxygen therapy	4.5 [2.5-7.0]	15.0 [5.0-17.0]	<0.05
Discharge form ICU in days	6.0 [5.0-10.8]	18.0 [7.5-25.0]	<0.05
Discharge home in days	18.0 [9.0-31.5]	28.0 [13.5-45.0]	0.44
Medical support at discharge [b]			
None	4 (67)	4 (44)	0.70
G-tube feeding	2 (33)	5 (56)	-

Data are expressed as median [interquartile range] or n (%).
G-tube: nasogastric tube; ICU: intensive care unit; o/e LHR: observed to expected lung-to-head ratio; VIS: vaso-active inotropic support; -: not applicable.
[a] Recorded continuously during ICU admission.
[b] Defined as ventilatory, oxygen, pharmaceutical, G-tube feeding.

DISCUSSION

In the group of patients with mild CDH, a prenatally planned SBA is feasible. We consider it safe, and it avoids overtreatment with potential adverse side effects. Although numbers are low, and data are collected retrospectively in a single centre, this suggests that individualised care in patients with CDH should be considered. By allowing SBA, iatrogenic complications due to prompt intubation and ventilation could be minimised. In addition, stress, pain, and the need for sedation is reduced in these infants; consequently, postnatal parent-infant interaction is improved. Delayed intubation did not seem to negatively affect outcomes. However, a larger prospective trial is needed to ensure that SBA is safe. Furthermore, we believe that this approach should only be done in expertise centres that have a multidisciplinary team of specialists caring for infants with CDH.

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7 | Spontaneous breathing approach in mild congenital diaphragmatic hernia: a resuscitation algorithm

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ABSTRACT

Background: Infants with a congenital diaphragmatic hernia (CDH) and expected mild pulmonary hypoplasia have an estimated survival rate of 90%. Current guidelines for delivery room management do not consider the individual patient's disease severity, but an individualised approach with spontaneous breathing instead of routine mechanical ventilation could be beneficial for the mildest cases. We developed a resuscitation algorithm for this individualised approach serving two purposes: improving the success rate by structuring the approach and providing a guideline for other centres.

Methods: An initial algorithm was discussed with all local stakeholders. Afterwards, the resulting algorithm was refined using input from international experts.

Results: Eligible CDH infants: left-sided defect, observed to expected lung-to-head ratio ≥50%, gestational age at birth ≥37.0 weeks, and no major associated structural or genetic abnormalities. To facilitate fetal-to-neonatal transition, we propose to start stabilisation with non-invasive respiratory support and to adjust this individually.

Conclusions: Infants with mild CDH might benefit from an individualised approach for neonatal resuscitation. Herein, we present an algorithm that could serve as guidance for centres implementing this.

INTRODUCTION

Around 70% of all infants with a congenital diaphragmatic hernia (CDH) are detected during prenatal screening.[1-3] This provides an opportunity for early referral to specialised centres, additional diagnostic procedures, and individualised counselling. For isolated cases, postnatal outcomes largely depend on the extent of the pulmonary disease.[4,5] Antenatal ultrasound measurement of the contralateral lung, expressed as the observed to expected lung-to-head ratio (o/e LHR), is the most validated method to estimate the severity of pulmonary hypoplasia.[4,5] Liver position and defect-side are additional independent predictors of postnatal outcomes.[3,4,6] Based on these parameters, one can distinguish a group with a relatively mild degree of pulmonary hypoplasia, corresponding with an estimated survival rate of 90%.[4,5] Current guidelines on delivery room management apply to all neonates with CDH and do not take the individual neonate's disease severity into account. An example of this is initial mechanical ventilation, which might be too aggressive for infants with expected mild pulmonary hypoplasia, given the favourable outcomes, the risk of ventilator-induced lung injury, and the stress caused by intubation.[3-5,7,8] A more individualised approach has the potential to avoid overtreatment and risks of intubation.

The Erasmus MC implemented a trial of spontaneous breathing for a specific subset of infants (isolated left-sided CDH, o/e LHR ≥50%, and intra-abdominal liver position) in December 2014.[9] A retrospective single-centre audit recently demonstrated that the spontaneous breathing approach (SBA) was feasible, but 60% of cases still required intubation in the first hours after birth.[10] On the other hand, there was an apparent decrease in the total length of hospital stay in successful cases and, more importantly, there were no adverse effects of the delayed intubation in cases that failed the SBA.[10] These results justify further evaluation of this approach. Yet, the low success rate in this small series highlights that optimal case selection is challenging and emphasises the need for a standardised management algorithm.[10] Meanwhile, other centres have already implemented the SBA or are interested. For these reasons, we developed a resuscitation algorithm that serves two purposes: improving the success rate by structuring the approach and providing a guideline for centres that consider implementation.

METHODS

Algorithm development was a two-step process: first, it was drafted and discussed by all stakeholders that are involved in the care of CDH infants in the Erasmus MC (i.e.

neonatal nurses, neonatologists, obstetricians, paediatric intensivists, and paediatric surgeons); second, the resulting algorithm was optimised with input from international experts on neonatal resuscitation, CDH management, and fetal/neonatal physiology. Medical ethical approval for prospective data collection was obtained in the Erasmus MC as the initiating centre (MEC-2021-0304) and will be obtained in all centres that start data collection.

RESULTS

Patient selection

Only CDH infants with expected mild pulmonary hypoplasia are considered candidates. We propose the following eligibility criteria depicted in Table 1. We recommend discussing the initial ventilation strategy for each case during a multidisciplinary meeting around 30 weeks of gestation, involving all caregivers.

Table 1 Eligibility criteria for spontaneous breathing approach

	Eligibility criteria
-	Left-sided defect;(3, 14)
-	o/e LHR ≥50% (measured on ultrasound at 30 weeks of gestational age [28-32 weeks] or on initial visit in case of detection after 30 weeks of gestational age) and abdominal liver position;(4, 5)
-	Gestational age at birth ≥37.0 weeks;(15)
-	No antenatal diagnosed major associated structural or genetic abnormalities.(16)

o/e LHR: observed to expected lung-to-head ratio.

Clinical algorithm

The primary aim of perinatal stabilisation of infants with a CDH is to establish adequate oxygenation whilst avoiding hypoxia, hyperoxia, and high peak airway pressures.[9,11] In the above-mentioned series, reasons for intubation in the delivery room were low SpO_2-levels, absence of breathing movements, or signs of respiratory distress.[10] To facilitate the fetal-to-neonatal transition, and, thus, the success of the SBA, we suggest to start stabilisation with non-invasive respiratory support and to adjust this individually (Figure 1). It is, however, not clear whether the fetal-to-neonatal transition in these infants is more favourably supported by additional FiO_2 and/or continuous distending airway pressures (high flow or CPAP). To enable implementation in other centres, we leave it up to the centre's discretion to decide whether high flow or CPAP is more feasible within their local logistics and standard of care. To minimise the negative effects of potential abdominal distension associated with non-invasive respiratory support, we recommend early insertion of an oro-/nasogastric tube.

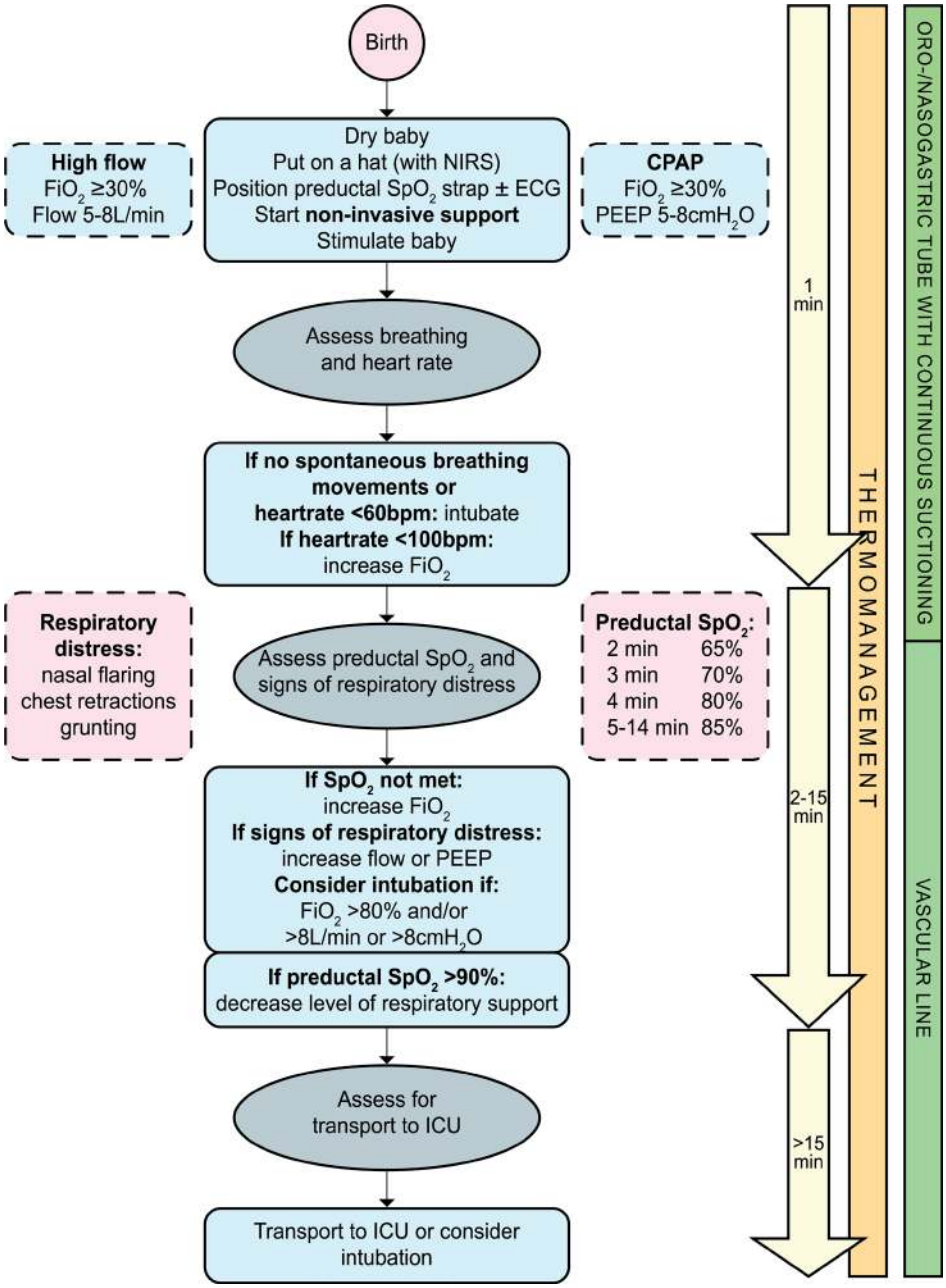

Figure 1 Flowchart spontaneous breathing approach for infants with a congenital diaphragmatic hernia.

We recommend to:

- Initiate nasal high flow or CPAP and subsequently titrate up or down by continuously evaluating the infant's respiratory status using the European Neonatal Life Support guidelines;[12]
- Consider intubation in case of insufficient spontaneous breathing movements, heart rate <60/min, FiO_2 >80%, flow >8 L/min, or CPAP >8 cmH_2O;
- Decrease the level of respiratory support if preductal SpO_2 >90%;
- Insert an oro-/nasogastric tube with continuous suctioning.

DISCUSSION

This resuscitation algorithm presents an individualised approach for infants with a CDH and predicted mild pulmonary hypoplasia. We acknowledge that the proposed algorithm is based on expert-opinion and low-grade, single-centre evidence (Scottish Intercollegiate Guidelines Network criteria, grade of recommendation D).[13] Ideally, this strategy should be tested in a randomised controlled trial. However, the lack of equipoise in centres that have already implemented the SBA would pose a challenge for reaching a sufficient sample size to evaluate the full extent of the various clinically relevant outcomes. Instead, prospective observational data collection of CDH infants cared for with the SBA is in progress within the framework of an international research consortium: the very mild CDH – SBA consortium (VeSBA). We share our algorithm, so that the SBA may be adopted by other centres and we invite their contribution to this prospective registry. We emphasise that strict adherence to the algorithm is not a prerequisite to join the VeSBA consortium and local adaptations are obviously acceptable.

CONCLUSION

Current guidelines on delivery room management for infants with a CDH do not take into account the individual patient's disease severity. However, the spontaneous breathing approach is an individualised approach for infants with a relatively mild CDH that could prevent overtreatment in this specific subgroup.

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8 | Sedation prior to intubation at birth in infants with congenital diaphragmatic hernia: an international survey on current practices

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ABSTRACT

Introduction: Infants with congenital diaphragmatic hernia (CDH) are commonly intubated immediately after birth. Consensus on whether to provide sedation prior to intubation in the delivery room is lacking, although avoidance of stress is especially important in this population with high risk of pulmonary hypertension. We aimed at obtaining an overview of local pharmacological interventions and at providing guidance on delivery room management.

Methods: An electronic survey was sent to international clinicians in referral centres for prenatal and postnatally diagnosed infants with CDH. This survey addressed demographic information, use of sedation and/or muscle relaxant prior to intubation, and use of pain scales in the delivery room.

Results: We received 93 relevant responses from 59 centres. Most centres were from Europe (n=33, 56%), followed by North America (n=16, 27%), Asia (n=6, 10%), Australia (n=2, 3%), and South America (n=2, 3%). A total of 19% (11/59) of the centres routinely provided sedation prior to intubation in the delivery room, with midazolam and fentanyl being most often used. Methods of administration varied for all medications provided. Only 5 of 11 centres using sedation reported an adequate sedative effect prior to intubation. Muscle relaxants prior to intubation were used in 12% (7/59) of the centres, although not always in combination with sedation.

Conclusion: This international survey shows a substantial variation in sedation practices in the delivery room and scarce use of both sedative agents and muscle relaxants prior to intubation of CDH infants. We provide guidance on developing protocols for pre-intubation medication in this population.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a rare condition characterised by incomplete closure of the diaphragm and herniation of abdominal organs into the fetal chest. After birth, many of those infants will experience respiratory insufficiency, often in combination with pulmonary hypertension. To avoid hypoxia and consequently worsening of the cardiorespiratory state, they often require respiratory support in the delivery room. As non-invasive ventilation strategies are not used due to concerns about bowel distension, intubation is often performed within the first minutes after birth.[1]

The timeframe for administering medication prior to endotracheal intubation is limited given the relative urgency of providing invasive respiratory support; as such, sedation is often given after securing the airway. However, awake intubation induces stress and pain, reflected by physiological responses such as bradycardia, hypoxia, and a rise in systemic arterial blood pressure and intracranial pressure.[2,3] Neonatal exposure to stress also affects long-term outcomes in experimental studies, warranting adequate pain treatment in newborns.[4] Pre-intubation sedation decreases the pain score, attenuates the negative physiological responses to intubation, minimises the risk of airway injury, and reduces the number of attempts till and time to successful intubation.[2] These are desirable outcomes in infants with CDH, as stress - including hypoxia - is an important trigger for pulmonary hypertension and endotracheal intubation is often challenging due to tracheal deviation.

The availability of guidelines on pre-intubation sedation in infants with CDH is limited: the CDH EURO Consortium guideline recommends to avoid neuromuscular blockade and to provide pre-intubation medication, but acknowledges that this is not always possible; the Canadian guideline recommends combining sedation with neuromuscular blockade in mechanically ventilated infants, although not specifically in the delivery room; the American guideline does not address delivery room management.[5-7] Furthermore, research considering methods of administration other than intravenous (IV) administration, such as intranasal (IN), intramuscular (IM), umbilical vein (UV), is lacking, although these methods could have a shorter time to action. In combination with a lack of consensus, this likely translates into a substantial variation in local practices hampering assessment of the optimal sedation strategy. In this study, we collected information on local practices in an international survey, aiming at defining future research directions and providing guidance on sedation prior to delivery room intubation in infants with CDH.

METHODS

This study was initiated by the Erasmus MC, Rotterdam, The Netherlands. Data were collected using an online survey developed in LimeSurvey (LimeSurvey GmbH, Hamburg, Germany). The validity of the content was ensured by pre-testing the survey by neonatologists working at the neonatal intensive care unit in the Erasmus MC and the Leiden University Medical Center. Based on their feedback, the survey was revised. The survey was distributed during the International Congenital Diaphragmatic Hernia Symposium in Glasgow (2022), via existing networks (*i.e.* ERNICA and CDH EURO), and via email. We aimed at collecting data on routine practices in as many centres as possible. The survey was accessible from April 2022 to August 2022. The topics addressed are demographic information, routine use of pre-intubation sedation and muscle relaxant in infants with CDH, reasons for premedication use, types of medication and methods of administering, use of pain scales in the delivery room, and ideas on how to improve the current intubation protocol for CDH infants. Supplementary material A provides the full-text survey questions. Responses from centres that are not involved in postnatal management of infants with CDH were excluded. In case of multiple responses from the same centre, the responses were combined to one response per centre. In case of major discrepancies between responses, we asked the respondents for clarification. Descriptive statistics are used to depict the results from the survey and data are presented as numbers (percentages).

RESULTS

Demographic information

Of 147 responses, 54 were excluded due to either no answers at all or no answers on the questions about sedation. The remaining 93 responses came from respondents working in 59 different centres. Those responses coming from respondents working in the *same centre* were combined into one response per centre, leaving the responses from 59 centres in 23 countries. Most centres were from Europe (55.9%, n=33), followed by North America (27.1%, n=16), Asia (10.2%, n=6), Australia (3.4%, n=2), and South America (3.4%, n=2). The caseload of CDH cases per year was <5 in 16.9% (n=10), 5-10 in 32.2% (n=19), 10-15 in 23.7% (n=14), and >15 in 27.1% (n=16).

Premedication in the delivery room in infants with CDH

Pre-intubation *sedation* in infants with CDH was routinely provided in 11 centres (18.6%) and not provided in 48 centres (81.4%). Table 1 depicts the routine premedication and whether premedication resulted in an adequate sedative effect prior to

intubation. The centre using IV ketamine reported the use of IM ketamine in case no IV access could be established. Only in five of eleven centres in which pre-intubation sedation was provided, an adequate sedative effect was observed prior to performing intubation. Seven of eleven centres reported a second choice of premedication: fentanyl IV/IN (n=2), midazolam UV/IV (n=2), ketamine UV (n=1), morphine UV (n=1), and propofol IV (n=1).

Table 1 Reported routine pre-intubation analgo-sedatives in infants with congenital diaphragmatic hernia

	First choice sedatives	Sedative effect prior to intubation [a]	Second choice sedatives
Centre 1	Fentanyl IV/UV	No	I don't know
Centre 2	Midazolam IN	I don't know	No
Centre 3	Fentanyl IV/UV	Yes	Midazolam UV
Centre 4	Ketamine IM	Yes	No
Centre 5	Fentanyl UV	No	Ketamine UV
Centre 6	Fentanyl IV	Yes	Midazolam IV
Centre 7	Midazolam IV	I don't know	Fentanyl IV
Centre 8	Midazolam UV	No	Morphine UV
Centre 9	Ketamine IV/IM	Yes	Propofol IV
Centre 10	Morphine IV	I don't know	No
Centre 11	Midazolam IN	Yes	Fentanyl IN

IM: intramuscular; IN: intranasal; IV: intravenous; UV: umbilical vein.
[a] Sedative effects prior to intubation as observed by respondents.

Reported reasons to use pre-intubation sedation were prevention of stress and/or pain (n=7) and facilitation of intubation (n=6). The most frequent reason not to use sedation was to avoid a delay in intubation (n=30). Other reasons were the lack of an available protocol for the use of sedation (n=6), no need to sedate the infant, especially in non-vigorous infants with severe pulmonary hypoplasia (n=2), and the risk of suppressing spontaneous breathing (n=4). Many centres not providing pre-intubation sedation stated the need to improve current management. Possible suggestions were implementing video registration, performing stabilisation with an intact umbilical cord, and considering alternative methods of administration, such as IN/IM/UV.

Muscle relaxants prior to intubation were used by 7 centres (11.9%) and not used by 50 centres (84.7%). Two centres were uncertain on their institutional policy. Overall, only four centres used a combination of a sedative and muscle relaxant, and thus three centres used a muscle relaxant without sedative. The reported muscle relaxants were rocuronium (IV/UV), vecuronium (IV/UV), and atracurium (IV/IM). Reported reasons

for the use of muscle relaxants were optimisation of intubation (n=4), avoidance of stress (n=1), prevention of thoracic rigidity caused by fentanyl (n=1), and prevention of spontaneous breathing and air entry into the stomach or bowel (n=1).

Pain scales in the delivery room

The use of pain scales to assess the infant□s level of (dis)comfort in the delivery room was limited to three hospitals. The mentioned scores are: Kölner Sedierungsbogen; Neonatal Pain, Agitation and Sedation Scale (N-PASS); Premature Infant Pain Profile (PIPP); and the Children's Revised Impact of Event scale (CRIES) score.

DISCUSSION

The actual positive effects of pre-intubation sedation have been clearly demonstrated, but our survey shows that premedication in the delivery room with either sedatives and/or muscle relaxants is very scarcely used in infants with CDH. Although many centres emphasised the need to improve current pain and stress management in this population, only 19% of the responding centres commonly use premedication, and between these centres, local practices vary widely.

The limited timespan between administering sedation and the moment of intubation inherently plays a role in premedication practices, with intubation often being successful within two minutes after birth.[8] This translates into the need for premedication with a short time till action, which is not the case for several of the currently used medications. This emphasises the need for evidence-based protocols considering aspects such as time till and duration of action and potential adverse cardiorespiratory effects.

Apart from the choice of medication, another important consideration is the method of administration. IV administration will usually have the quickest effect but establishing IV access prior to intubation can be challenging and it can induce neonatal stress. An alternative could be using the umbilical cord to administer medication; however, this might not be preferable when the infant is stabilised with an intact cord – an intervention that is currently under investigation in two randomised trials.[9,10] On the other hand, we can speculate that the advantage of infants still having the benefits of being oxygenated via the placental gas exchange might provide a larger window for administering pre-intubation sedation.

The opioid fentanyl is used by almost one-third of our respondents providing pre-intubation analgesia and potential sedation. In general, IV fentanyl has a rapid effect, i.e. within one minute, and it exerts minimal haemodynamic side effects.[11,12] However, one major concern is the rigid chest syndrome, especially after fast infusion, which could be treated with either naloxone or muscle relaxants.[13] The onset of action of fentanyl IN and IM is suggested to be 5-10 minutes and 7-8 minutes, respectively, reducing their applicability in the delivery room.[12] A faster alternative is remifentanil, with an onset of action of three minutes in case of IN administration and a duration of action of less than six minutes.[12] However, remifentanil is more difficult to titrate and has a high risk on chest wall rigidity.[14]

Another agent reported by a third of the centres is midazolam, a benzodiazepine with effect within two minutes when administered IV and five minutes when administered IN.[12] A potential disadvantage of midazolam includes haemodynamic effects such as hypotension, decreased cardiac output, and decreased cerebral blood flow velocity.[2,15] Responding centres tend to combine midazolam with morphine or fentanyl, but studies support a potential better effect on pain and stress when using fentanyl as compared to morphine.[3,12] With morphine having both an unacceptable long time till action (>5-15 minutes) and known negative effects on neonatal haemodynamics, including hypotension and bradycardia, its use prior to urgent intubation is obsolete.[16,17]

Two centres reported using ketamine as pre-intubation sedation, and interestingly, both centres report a sedative effect of IM ketamine prior to intubation. IM ketamine has been shown to result in significantly decreased levels of pain and distress in infants and a longer duration of action when compared to IV ketamine.[18] Although IM ketamine might have a longer time till action than IV ketamine, the latter has a rapid onset of action <1 minute.[19] Potential side-effects of ketamine, such as hallucinations in older patients and decreases in arterial blood pressure, cannot be ruled out, but no major side-effects were observed in earlier trials in neonates.[19,20]

An alternative method to reach sedation in the infant immediately after birth could potentially be to administer medication to the mother before birth of the infant. None of the responding centres are currently using this method of sedation. A potential candidate could be pethidine, an opioid often used for relief of labour pain, although it might have limited efficacy.[21,22] Maternal sedation during labour is unwanted, and reassuringly, most studies did not show a strong sedative effect during labour.[23,24] Other than that, pethidine can result in neonatal side-effects, such as respiratory depression and a decreased alertness after birth.[21] However, these potential side-

effects might actually be favourable in infants with CDH as respiratory depression and decreased alertness could facilitate intubation.

Approximately one-third of the centres using pre-intubation sedation also administer muscle relaxants prior to intubation. However, some centres reported the use of muscle relaxants *without* sedation, a practice that is deemed highly questionable. The positive effects of specific sedatives are known to increase when combined with muscle relaxants, an example being fentanyl.[12] Also, a lower incidence of adverse events was reported when performing intubation after administering a combination of sedation and neuromuscular blockade rather than just sedation.[25] Muscle relaxants with a possible onset of action within minutes include agents reported in our survey, such as rocuronium (1-3 minutes) and vecuronium (2-3 minutes), but this all concerns IV administration.[12] Although rocuronium could be administered IM, its onset of action increases to seven minutes.[12] With vecuronium having a slow elimination phase and thus a long duration of effect, its use in an acute setting seems limited.[26]

One could also argue that rescue intubation without sedation might be acceptable in non-vigorous infants, as it has been suggested that this subgroup will likely only experience the negative effects on the cardiorespiratory system without having the benefits of sedation. In vigorous infants, on the other hand, pain scales or sedation scales could aid in establishing the level of (dis)comfort in the delivery room and thus the need for premedication. The scales mentioned in our survey are, however, not validated for the assessment of either (dis)comfort in the delivery room or the effect of pre-intubation sedation.[27,28] We suggest using the Intubation Readiness Score that could assist in establishing the optimal moment to intubate after providing sedation.[27]

Our data clearly demonstrate that immediate intubation of almost all CDH infants, as dictated by most guideline, often results in awake intubation. This potentially causes neonatal stress and pain but also negative effects on the long-term, although further research would be required to evaluate differences between centres with different sedation practices. We hypothesise that a change of the standard of care interventions after birth could optimise the transition period by avoiding neonatal stress and pain. A combination of delayed cord clamping, early positioning of an oro-/nasogastric tube with continuous suctioning, and initiating non-invasive respiratory support after birth, such as high flow or continuous positive airway pressure, would provide a larger timespan to administer premedication without the problem of bowel distension. Intubation should then only be done after reaching adequate sedation and muscle relaxation. As premedication reduces the time till successful intubation, we speculate that this changed approach might not have a significant impact on the

time till successful intubation. Given the lack of studies on non-invasive ventilation in infants with CDH and the current dogma of required primary intubation, we cannot provide clear recommendations on the use of this modality. We emphasise that this approach should only be used in vigorous infants with spontaneous breathing and that non-invasive respiratory support should be adjusted to the individual infant's needs.

Considering the results of our survey, including the questionable choices on pre-intubation medication and existing literature, we have created an overview with guidance on clinical practice and current knowledge gaps (Figure 1). However, it may not be possible to address all questions by means of a randomised controlled trial given the issues performing such studies in rare diseases (slow recruitment, long trial periods, and multicentre design). Prospective data collection in international registries could be considered an alternative to overcome some of these hurdles and to inspire innovations in perinatal stabilisation.

To the best of our knowledge, this is the first study collecting data on local practices regarding pre-intubation medication in infants with CDH. We were able to collect responses from large referral centres across the world with expertise on the management of infants with CDH. Our results are probably most representative of European practices, as the majority of the respondents work in centres across Europe. Another limitation inherent to any survey research is the potential of recall bias; however, we expect that the impact will be limited as most respondents work in centres with a relatively high number of CDH cases per year. On top of that, several responses were combined as certain centres were represented by more than one respondent, providing a validation of their responses.

CONCLUSION

The lack of consensus on the use of sedation prior to intubation translates into variation in clinical practices in infants with CDH across the world. In fact, despite clearly described negative effects of awake intubation, premedication in infants with CDH is only used in a minority of centres. Although innovations such as delayed cord clamping could aid the perinatal transition and increase the timespan to provide sedation, further research and guidelines on both the optimal pre-intubation medication strategies and optimal sequence of interventions after birth are warranted.

	Timing	Sedative	Effect evaluation	Muscle relaxant	Intubation	Optimisation
Admission of woman pregnant with fetus with congenital diaphragmatic hernia (CDH)	**Goal** To achieve a sedative effect in the infant before intubation is attempted by administering drugs at the right time	**Goal** To achieve adequate sedation with limited effects on perinatal transition	**Goal** To establish moment of optimal sedation in order to intubate	**Goal** To facilitate intubation and enhance the effect of sedatives	**Goal** To avoid hypoxia after birth	**Goal** To improve existing protocols and to enable education and quality improvement
	Guidance Use a method of administering drugs that is easy to use and results in a short time till action	**Guidance** Use fast acting drug (i.e. remifentanil, fentanyl, midazolam) with limited side-effects	**Guidance** Use Intubation Readiness Score (IRS) or other validated sedation scale	**Guidance** Use fast acting muscle relaxant with short duration of action (i.e. rocuronium, atracurium)	**Guidance** Intubate immediately in non-vigorous infants; intubate after reaching adequate sedation in vigorous infants	**Guidance** Record delivery room management and analyse post-hoc to improve protocols
	Gaps -Patient selection -Fastest method of administration (i.e. intranasal, via the mother) -Safety	**Gaps** -Patient selection -Choice of medication -Effects on perinatal transition	**Gaps** -Appropriate comfort scale for (dis)comfort in the delivery room -Validity of IRS in infants with CDH	**Gaps** -Choice of medication -Optimal method of administration	**Gaps** -Effects of non-invasive respiratory support instead of immediate mechanical ventilation	**Gaps** -Effectiveness -Implementation of video recordings in the delivery room

Figure 1 Guidance on clinical practice and overview of current knowledge gaps in pre-intubation medication practices in infants with congenital diaphragmatic hernia.

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SUPPLEMENTARY MATERIAL A. FULL TEXT SURVEY QUESTIONS.

DEMOGRAPHICS

1. In which country do you work?

2. In which hospital do you work?

3. How many infants born with CDH are approximately treated in your hospital per year?

(a) <5;

(b) 5-10;

(c) 10-15;

(d) >15;

(e) I don't know.

SEDATION PRIOR TO INTUBATION OF CDH INFANTS

4. Do you routinely administer sedation prior to intubation of CDH infants in the delivery room (such as midazolam)?

(a) Yes, to the baby;

(b) Yes, to the mother;

(c) No;

(d) I don't know.

If '(a) Yes, to the baby':

4a1. Please indicate the main consideration to use sedation?

4a2. Please specify which medication is primarily used?

(a) Midazolam;

(b) Lorazepam;

(c) Ketamine;

(d) Pentobarbital;

(e) Phenobarbital;

(f) Dexmedetomidine;

(g) Clonidine;

(h) Opioids;

(i) Other.

4a2h. Which opioid is primarily used?

(a) Fentanyl;

(b) Morphine;

(c) Diamorphine;

(d) Meperidine;

(e) Hydromorphone;

(f) Methadone;

(g) Other.

4a3. Which starting dose is used in the delivery room?

4a4. Please specify the route of administration?

(a) Intravenous;

(b) Umbilical vein;

(c) Buccal;

(d) Intranasal;

(e) Intramuscular;

(f) I don't know;

(g) Other.

4a5. Please describe why this combination of medication and route of administration is your first choice?

4a6. Do you usually see a sedative effect in the infant prior to intubation?

(a) Yes;

(b) No;

(c) I don't know.

4a7. Is there a second choice sedative agent that you would use prior to intubation of CDH infants in the delivery room?

(a) Yes;

(b) No;

(c) I don't know.

4a7a1. Please specify which drug is your second choice agent?

(a) Midazolam;

(b) Lorazepam;

(c) Ketamine;

(d) Pentobarbital;

(e) Phenobarbital;

(f) Dexmedetomidine;

(g) Clonidine;

(h) Opioids;

(i) Other.

4a7a1h1. Which opioid is your second choice agent?

(a) Fentanyl;

(b) Morphine;

(c) Diamorphine;

(d) Meperidine;

(e) Hydromorphone;

(f) Methadone;

(g) Other.

4a7a2. Please indicate the route of administration?

(a) Intravenous;

(b) Umbilical vein;

(c) Buccal;

(d) Intranasal;

(e) Intramuscular;

(f) I don't know;

(g) Other.

If '(b) Yes, to the mother':

4b1. Which medication do you use (and which dosage)?

4b2. Which route of administration is primarily used?

4b3. Do you usually see a sedative effect in the infant prior to intubation?

(a) Yes;

(b) No;

(c) I don't know.

If '(c) No':

4c1. Please indicate the main consideration not to use sedation?

MUSCLE RELAXATION PRIOR TO INTUBATION OF CDH INFANTS

5. Do you routinely use muscle relaxation prior to intubation of CDH infants in the delivery room?

(a) Yes;

(b) No;

(c) I don't know.

If '(a) Yes':

5a1. Please indicate the main consideration to use muscle relaxation?

5a2. Please specify which medication is primarily used?

5a3. Please specify the route of administration?

ADDITIONAL QUESTIONS

6. Do you routinely use a pain/sedation score to assess the infant's level of comfort/discomfort in the delivery room?

(a) Yes;

(b) No;

(c) I don't know.

If '(a) Yes':

6a1. Which scoring system?

7. Do you routinely video record stabilisation in the delivery room?

(a) Yes;

(b) No;

(c) I don't know.

8. Do you think that the current pain/stress management in CDH infants at the time of birth and intubation should be improved? If yes, how?

9. Would you give us permission to contact you in the future for any additional questions via your email address?

(a) Yes;

(b) No;

(c) I don't know.

If '(a) Yes':

9a1. Please write down your email address below?

PART III

| After birth |

9 | Fetoplacental vascular reactivity is altered in fetuses with congenital diaphragmatic hernia

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Submitted

10 | Oxygen saturation index in neonates with a congenital diaphragmatic hernia: a retrospective cohort study

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ABSTRACT

Introduction: The oxygenation index (OI) is a marker for respiratory disease severity and adverse neonatal outcomes. The oxygen saturation index (OSI) is an alternative that allows for continuous non-invasive monitoring, but evidence for clinical use in critically ill neonates is scarce. The aim of this study was to evaluate the OSI as compared to the OI in term neonates with a congenital diaphragmatic hernia (CDH).

Methods: A single-centre retrospective cohort study was conducted including all live born infants with an isolated CDH between June 2017 and December 2020. Paired values of the OI and OSI in the first 24 hours after birth were collected. The relation between OI and OSI measurements was assessed, taking into account arterial pH, body temperature, and preductal versus postductal location of oxygen saturation measurement or arterial blood sampling. The predictive values for pulmonary hypertension, need for extracorporeal membrane oxygenation therapy, and survival at discharge were evaluated.

Results: Of 33 subjects included, 398 paired values of the OI (median 5.8 [3.3-17.2]) and OSI (median 7.3 [3.6-14.4]) were collected. The OI and OSI correlated strongly ($r=0.77$, $p<0.001$). The OSI values corresponding to the clinically relevant OI values (10, 15, 20, and 40) were 8.9, 10.9, 12.9, and 20.9, respectively. The predictive values of the OI and OSI were comparable for all adverse neonatal outcomes. No difference was found in the area under the receiver operating characteristic curves for the OI and the OSI for adverse neonatal outcomes.

Conclusions: The OSI could replace the OI in clinical practice in infants with a CDH.

INTRODUCTION

Respiratory insufficiency and pulmonary hypertension are common life-threatening complications in neonates born with a congenital diaphragmatic hernia (CDH).[1,2] Postnatal management is guided by several factors, such as echocardiography, physiological parameters (e.g. blood pressure), blood gas analyses, and the oxygenation index (OI). The OI is a respiratory parameter used to assess the severity of respiratory failure and to evaluate the efficacy of pulmonary vasodilators (such as inhaled nitric oxide [iNO]). In patients with a CDH, the OI is a leading criterion to administer iNO or to initiate extracorporeal membrane oxygenation (ECMO) therapy.[3-6] In addition, the OI on the first day of life is a predictor for adverse neonatal outcomes, such as mortality and pulmonary morbidity.[6-10] Early identification of infants with a high risk of adverse outcomes could guide treatment and aid parental counselling.

The OI is calculated based on the mean airway pressure (MAP), the fraction of inspired oxygen (FiO_2), and the partial arterial pressure of oxygen (PaO_2).[8] By combining the oxygen delivery (MAP and FiO_2) and oxygen diffusion (PaO_2), the OI reliably reflects the patient's respiratory status.[6] However, a major disadvantage in using the OI is that it cannot be monitored continuously as it requires arterial blood sampling to determine the PaO_2.[3-5] In neonates with hypoxaemic respiratory failure, the oxygen saturation index (OSI) is proposed as a reliable alternative that uses the oxygen saturation (SpO_2) instead of the PaO_2.[3-5,11] As such, the OSI could continuously monitor the infant's respiratory status and predict adverse neonatal outcomes.[3-5,11-13] Continuous bedside monitoring enables tailored therapies (such as respiratory support and the use of pulmonary vasodilators) to the patient's changing individual needs, thereby preventing both hypoxia as well as hyperoxia.

To date, reports on the clinical use of the OSI in critically ill neonates are scarce. Our study addresses this knowledge gap by evaluating the OSI in neonates with a CDH. We hypothesised that OI and OSI are related and can be used interchangeably in CDH infants, especially when the SpO_2 and PaO_2 measurements are taken at the same location (preductal or postductal). In addition, we aimed to determine the predictive value of the OSI as an early marker for adverse neonatal outcomes.

METHODS

Study cohort

We performed a single-centre retrospective cohort study at Erasmus MC, University Medical Centre (Rotterdam, The Netherlands), a tertiary referral centre. We included all consecutive live born cases with an isolated CDH between June 2017 and December 2020. We excluded infants with associated anomalies that would directly influence postnatal outcomes, out-born infants, infants receiving palliative care, infants with bilateral CDH or a diaphragmatic eventration, and infants who were not intubated in the delivery room (shown in Figure 1). The research protocol was approved by the local medical Ethical Committee, and informed consent was waived.

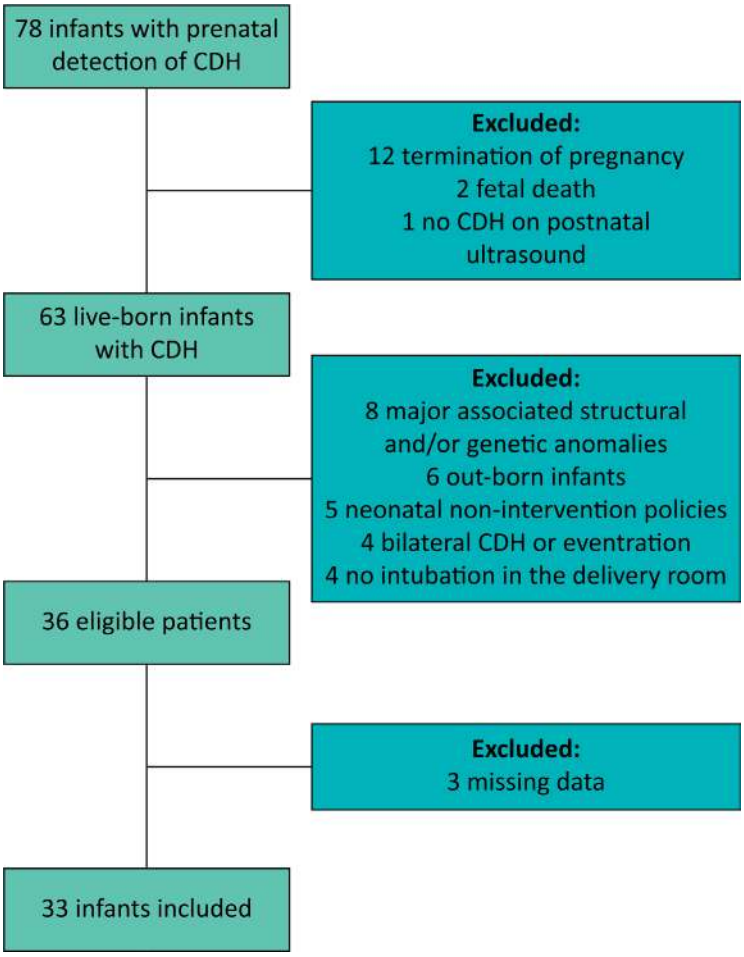

Figure 1 Flowchart of inclusion. CDH, congenital diaphragmatic hernia.

Data collection

Baseline characteristics for each patient included gender, gestational age at birth, birth weight, Apgar score at 5 minutes, umbilical artery pH, prenatal ultrasound measurements of observed to expected lung-to-head-ratio (o/e LHR) and liver position, side and classification of the diaphragmatic defect, and age at surgical repair.[14] Results from arterial blood samples in the first 24 hours after birth were documented together with ventilator settings (i.e. MAP and FiO_2), preductal and postductal SpO_2 levels, and body temperature at the time of arterial blood sampling. The OI was calculated as follows: OI = FiO_2 [%] x MAP [cmH_2O]/PaO_2 [mmHg].[8] The OSI was calculated as follows: OSI = FiO_2 [%] x MAP [cmH_2O]/SpO_2 [%].[11] Adverse neonatal outcomes included pulmonary hypertension, need for ECMO therapy, and survival at discharge. Pulmonary hypertension was defined as an estimated right ventricular systolic pressure to systolic blood pressure ratio of ≥2/3 on echocardiography, which required therapy.[15]

OI and OSI values were paired taking into consideration a minimal time difference between measurements; for the vast majority this was within seconds as continuous data were collected. If possible, we combined preductal OI values (preductal PaO_2) with preductal OSI values (preductal SpO_2) and postductal OI values (postductal PaO_2) with postductal OSI values (postductal SpO_2) (*matched* OI-OSI pairs). If we could not match a preductal OI value with a preductal OSI value because of incomplete data, we used the postductal OSI value; if we could not match a postductal OI value with a postductal OSI value because of incomplete data, we used the preductal OSI value (*unmatched* OI-OSI pairs). For each patient we also determined the OI and OSI values at admission to the intensive care unit (<3 hours after birth) and the highest (worst) OI and OSI values in the first 24 hours after birth as we expected that these values could be clinically useful in predicting neonatal outcomes.[6,8,10]

Local protocol

Our local protocol is based on the CDH EURO Consortium guideline, which recommends to administer iNO in neonates with an OI >20 and to consider ECMO therapy in neonates with an OI ≥40 persisting for ≥3 hours.[16] In our centre, the OI is, among others, one of the criteria that are used in considering ECMO therapy in infants with a CDH.

Statistical analysis

Normality of the data was checked with QQ-plots and density distributions combined with the Shapiro-Wilk test. The correlation coefficient of the repeated measurements of the OI and OSI was calculated separately for all pairs, the matched pairs, and the

unmatched pairs using the R package "rmcorr". A Spearman correlation coefficient was calculated for the correlation between the OI and OSI values at admission, and the highest OI and OSI values in the first 24 hours after birth.

Using linear mixed models, we derived a predictive equation for the association of the OSI with the OI while taking into account the correlation within individuals. Multivariate mixed models were used to correct for both pH and body temperature that both affect the oxygen dissociation curve. The best fitting model was determined with ANOVA tests. We used the predictive equation with the best fit and highest clinical relevance to calculate the corresponding OSI cut-off values for relevant OI values. Based on the guidelines, local clinical practice, and other studies assessing the predictive value of the OI, we selected OI values of 10, 15, 20, and 40.[3,5,10,16,17] These values and the corresponding OSI values were then used to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the outcomes pulmonary hypertension, ECMO, and mortality. Receiver operator characteristic (ROC) curves and areas under the curve (AUC) further assessed the discriminative ability of the OI and OSI for the adverse neonatal outcomes using the R package "pROC". A sensitivity analysis in three subgroups (preductal matched pairs, postductal matched pairs, and unmatched pairs) was performed to evaluate potential bias introduced by combining all data in our mixed model analysis.

Statistical analyses were performed using the computing environment R (v4.0.2; R Core Team [2020], Vienna, Austria). $P<0.05$ was considered as the level of significance.

RESULTS

Baseline characteristics

The total study population included 33 neonates with a CDH, of whom 3 infants were diagnosed with minor associated abnormalities (i.e. mosaicism chromosome 7, unilateral renal agenesis, and radial aplasia; the latter two with normal genetic analysis on microarray and whole exome sequencing). Table 1 provides an overview of the baseline characteristics of all included subjects.

Table 1 Baseline characteristics

	n	All subjects (n=33)
Fetal characteristics		
o/e LHR (%)	33	44.3 ± 12.0
Gestational age at measurement (weeks^{+days})	33	26^{+6} [26^{+0}-29^{+3}]
Intrathoracic liver	33	17 (52)
Left-sided defect	33	28 (85)
Neonatal characteristics		
Male	33	19 (58)
Gestational age at birth (weeks^{+days})	33	38^{+1} [37^{+5}-38^{+2}]
Birthweight (g)	33	3000 [2700-3200]
Birthweight centile (%)	33	34 [18-61]
Apgar 5'	26	7 [6-8]
Umbilical artery pH	31	7.26 ± 0.08
Age at surgical repair (days)	32	6 [5-8]
Defect size	33	
A		3 (9)
B		10 (30)
C		8 (24)
D		7 (21)
Unknown		5 (15)

Data are expressed as mean ± standard deviation, median [interquartile range] or n (%).o/e LHR: observed to expected lung-to-head ratio.

Pairs of OI values and OSI values

We calculated 406 OI values (327 preductal and 79 postductal) and 700 OSI values (309 preductal and 391 postductal). Preductal OI values were compared to preductal (n=245, *matched*) or postductal (n=80, *unmatched*) OSI values; for 2 preductal OI values, this was not possible due to missing SpO_2 values. Postductal OI values were compared to postductal OSI values (n=73, *matched*); this was not possible for 2 postductal OI values due to missing SpO_2 measurements. Additionally, we excluded 4 unmatched pairs of postductal OI values and preductal OSI values as they only accounted for <1% of the total data set. This resulted in a total of 398 paired OI and OSI values, with a median OI of 5.8 [3.3-17.2] and a median OSI of 7.3 [3.6-14.4]. Table 2 contains the characteristics of the variables that are used in the statistical analyses, and Supplementary Table 1 contains the characteristics of the preductal matched pairs and postductal matched pairs.

Table 2 Characteristics of data used in statistical analyses

	Total group		Matched pairs		Unmatched pairs	
	n	(n=398)	n	(n=318)	n	(n=80)
pH	398	7.25 [7.19-7.30]	318	7.26 [7.20-7.30]	80	7.24 [7.14-7.32]
PaO_2 (mmHg)	398	85.5 [57.9-130.3]	318	93.4 [62.3-134.1]	80	68.6 [47.8-105.0]
FiO_2 (%)	398	53 [35-100]	318	51 [37-99]	80	88 [25-100]
MAP (cmH_2O)	398	12.7 [10.8-14.8]	318	12.6 [10.8-14.4]	80	13.7 [10.9-16.1]
Preductal SpO_2 (%)	245	97 [93-99]	245	97 [93-99]	80	
Postductal SpO_2 (%)	153	94 [79-99]	73	96 [90-99]	80	91 [76-97]
Body temperature (°C)	398	37.0 [36.8-37.4]	318	37.0 [36.8-37.3]	80	37.0 [36.8-37.4]
Oxygenation index	398	5.8 [3.3-17.2]	318	5.4 [3.3-13.6]	80	9.5 [3.6-27.8]
Oxygen saturation index	398	7.3 [3.6-14.3]	318	7.1 [3.8-12.6]	80	12.4 [3.1-21.8]

Data are expressed as median [interquartile range]. Data on preductal matched pairs and postductal matched pairs separately are shown in Supplementary Table 1.
PaO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; MAP: mean airway pressure; SpO_2: oxygen saturation; OI: oxygenation index; OSI: oxygen saturation index

Correlation of OI and OSI

OI and OSI values were strongly correlated: all pairs (r=0.77, p<0.001), matched pairs (r=0.73, p<0.001), and unmatched pairs (r=0.76, p<0.001). The correlation of OI and OSI values was also strong at admission (r_s=0.79, p<0.001) and was strongest for the highest OI and OSI values in the first 24 hours (r_s=0.93, p<0.001).

Association between OI and OSI

Table 3 presents the regression formulas describing the association between OI and OSI values in infants with a CDH. In all analyses, the OI was significantly and strongly associated to the OSI (p<0.001). Adding pH to the model improved the fit of the model significantly (p<0.001), but adding body temperature did not (p=0.35).

Table 3 Mixed models on the OSI in the total group

	Intercept		Oxygenation index		pH		Temperature	
	Ƀ	*p*	Ƀ	*p*	Ƀ	*p*	Ƀ	*p*
398 pairs	4.09	<0.001	0.44	<0.001				
33 groups	92.58	<0.001	0.40	<0.001	-12.08	<0.001		
	106.18	<0.001	0.38	<0.001	-15.57	<0.001	0.31	0.36

Ƀ reflects the change in the OSI for a one-unit increase in the corresponding predicting variable (i.e., OI, pH, and temperature). OI: oxygenation index; OSI: oxygen saturation index.

OSI cut-off values

The multivariate mixed model with the OI and the pH as independent variables fitted the data best. We thus calculated OSI values that correspond with OI values based on this model while assuming a mean pH of 7.25 (Table 2). OSI values corresponding with relevant OI values (10, 15, 20, and 40) were 8.9, 10.9, 12.9, and 20.9. For practical use, we rounded these values to 9, 11, 13, and 21.

Adverse neonatal outcomes

Of all subjects, 67% developed pulmonary hypertension, 33% required ECMO therapy, and 15% did not survive until discharge. Table 4 shows that the sensitivity, specificity, PPV, and NPV of the OI and OSI values at admission and highest OI and OSI values are comparable. Figure 2 shows the ROC curves for the OI and OSI values at admission and highest OI and OSI values in discrimination for adverse neonatal outcomes. The discriminative ability of the OI and OSI at admission was not different in prediction of pulmonary hypertension (AUC_{OI}=0.61 vs AUC_{OSI}=0.71, p=0.25), ECMO therapy (AUC_{OI}=0.78 vs AUC_{OSI}=0.82, p=0.68), and survival at discharge (AUC_{OI}=0.88 vs AUC_{OSI}=0.98, p=0.35). The discriminative ability of the highest OI and OSI was also not different in prediction of pulmonary hypertension requiring therapy (AUC_{OI}=0.83 vs AUC_{OSI}=0.90, p=0.11), ECMO therapy (AUC_{OI}=0.89 vs AUC_{OSI}=0.88, p=0.85), and survival at discharge (AUC_{OI}=0.86 vs AUC_{OSI}=0.91, p=0.18).

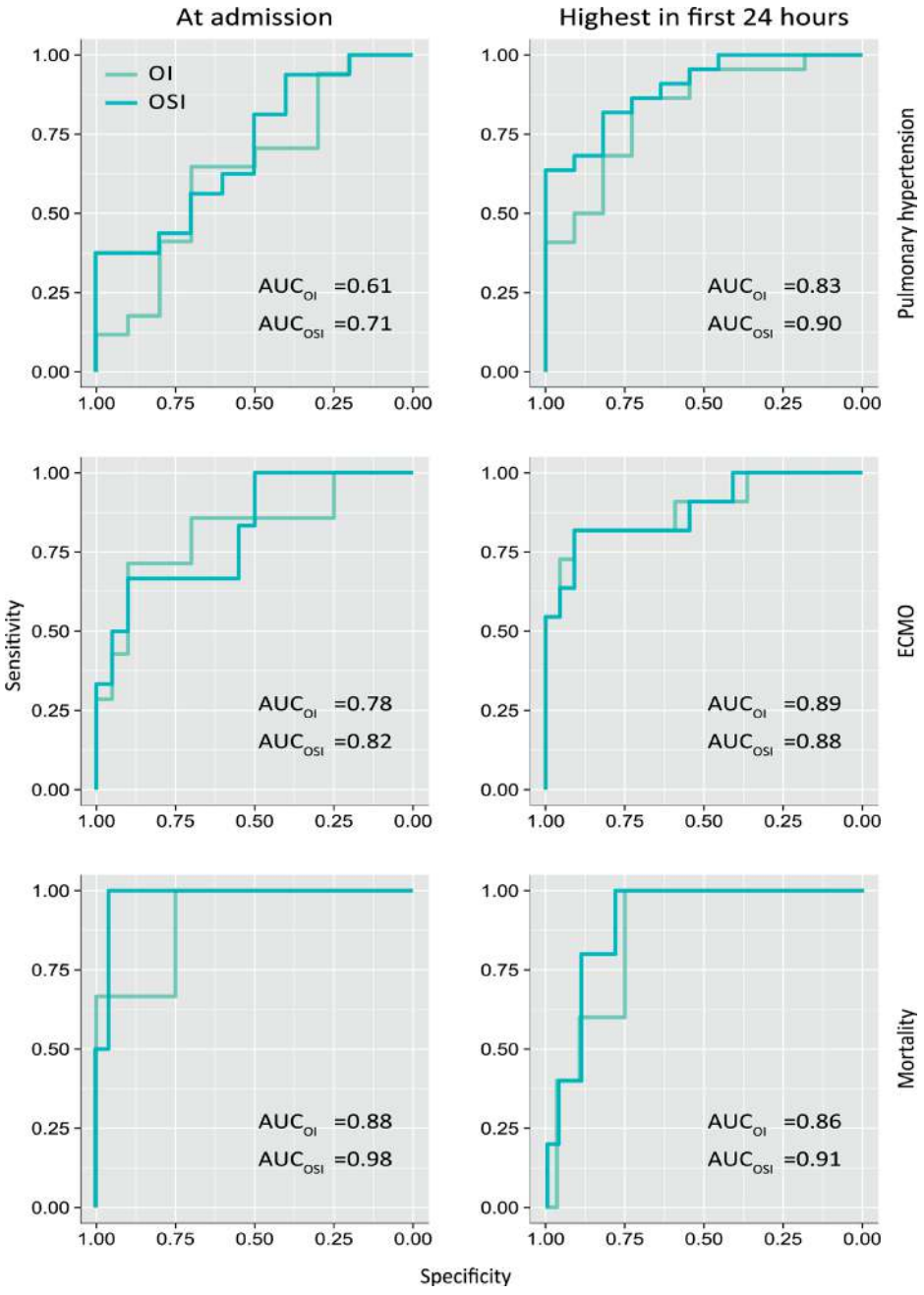

Figure 2 ROC curves of OI and OSI. ROC: receiver operating characteristic; OI: oxygenation index; OSI: oxygen saturation index; AUC: area under the curve; ECMO: extracorporeal membrane oxygenation.

Table 4 Predictive values of the OI and OSI

	At admission								Highest in first 24 hours							
	Oxygenation index				Oxygen saturation index				Oxygenation index				Oxygen saturation index			
	10	15	20	40	9	11	13	21	10	15	20	40	9	11	13	21
PH																
Sensitivity (%)	47	41	41	12	44	44	38	13	77	73	64	32	82	82	64	36
Specificity (%)	70	70	80	100	70	80	90	100	73	73	82	100	73	82	91	100
PPV (%)	73	70	78	100	70	78	86	100	85	84	88	100	86	90	93	100
NPV (%)	44	41	44	40	44	47	47	42	62	57	53	42	67	69	56	44
ECMO																
Sensitivity (%)	71	71	71	29	67	67	67	33	91	91	82	55	91	91	82	64
Specificity (%)	70	75	80	100	70	75	85	100	55	59	68	96	50	55	73	96
PPV (%)	46	50	56	100	40	44	57	100	50	53	56	86	48	50	60	88
NPV (%)	88	88	89	80	88	88	90	83	92	93	88	81	92	92	89	84
Mortality																
Sensitivity (%)	100	100	100	67	100	100	100	50	100	100	100	60	100	100	100	80
Specificity (%)	67	71	75	100	67	71	79	96	46	50	61	86	43	46	64	86
PPV (%)	27	30	33	100	20	22	29	50	25	26	31	43	24	25	33	50
NPV (%)	100	100	100	96	100	100	100	96	100	100	100	92	100	100	100	96

ECMO: extracorporeal membrane oxygenation; NPV: negative predictive value; OI: oxygenation index; OSI: oxygen saturation index; PPV: positive predictive value.

Sensitivity analysis

Multivariate mixed models with the OI and the pH as independent variables show a significant association between OI and OSI in each subgroup (Supplementary Table 2). The effect size and direction of these associations are in line with the results in the total group (Table 3).

DISCUSSION

We found strong correlations between OI and OSI values calculated in the first 24 hours after birth in neonates born with a CDH. Based on our models, we have determined that the clinically relevant OI values of 10, 15, 20, and 40 correspond to the OSI values of 9, 11, 13, and 21, respectively. The OI and OSI at admission and the highest OI and OSI in the first 24 hours after birth show similar sensitivity, specificity, and predictive values for major adverse neonatal outcomes. These findings highlight that the OSI could replace the OI in clinical practice, thereby enabling continuous real-time non-invasive monitoring of the infant's respiratory status and potentially diminishing the need for arterial blood sampling.

The strong positive correlation between OI values and OSI values is in line with earlier findings in infants with hypoxaemic respiratory failure.[3,5,17] Interestingly, our data suggest that whether the locations of PaO_2 and SpO_2 measurement are identical (pre- or postductal) does not importantly influence the strength of the correlation. In addition, the highest OI and OSI values correlated stronger than the overall OI and OSI values. An explanation for this may be found in SpO_2 and PaO_2 only having a linear relation in the middle part of the oxygen dissociation curve. Hence, at higher SpO_2 values, the correlation may be weaker, as was shown in a previous series in mechanically ventilated neonates in which a stronger correlation was observed when excluding SpO_2 values >98%.[17] This observation was also supported by a more recent study showing that OI and OSI correlated strongest if SpO_2 was 85-95% compared to that with values above 95%.[3] Due to our limited sample size, we refrained from subgroup analyses in those with SpO_2 >95% (present in 53% of the pairs).

The direction and effect size of the linear association between the OI and OSI are comparable to those observed in neonates with hypoxaemic respiratory failure.[3,5,17] Our data confirm that a two-unit increase of the OI correlates to about a one-unit increase of the OSI. However, methodological differences, particularly in measurement units, hamper comparison of our exact findings to previous series that reported slightly higher [18] or lower [4,5,17] OSI-to-OI ratios. Although we expected an effect on

the oxygen dissociation curve, body temperature did not significantly change the OSI values. Lower pH values were associated with higher OSI values, reflecting a left shift in the oxygen dissociation curve.[18] For practical use, we opted for a fixed pH value to determine OSI values that correspond to clinically relevant OI values.

Based on the strong linear relation between the OI and OSI, we speculate that the OSI cut-offs could be used as an alternative to the OI cut-offs used in clinical practice. We propose to use the OSI values of 9, 11, 13, and 21, corresponding to the, respective, OI values of 10, 15, 20, and 40. Prospective validation of these cut-offs in a larger sample size could further increase the clinical relevance and determine potential differences in cut-offs when using either preductal or postductal SpO_2 measurements. Furthermore, a high initial OSI value at admission to the intensive care unit could alert clinicians to an increased risk of a complicated postnatal course.

The OI is a strong predictor of outcomes in neonates with a CDH: the lowest (best) and mean OI in the first 24 hours and highest OI in the first 48 hours after birth accurately predict mortality.[7-10] The lowest OI might reflect a transient period of overtreatment instead of overall lung function.[6,7] Therefore, we did not evaluate the lowest OI, but focused on the highest and initial values. The predictive value and discriminative ability of the OI and OSI were comparable in our data; however, specifically the *highest* OSI showed a slightly higher predictive value for most adverse neonatal outcomes. This trend was consistent in almost all analyses, translating in higher AUCs for most outcomes. Although we did not document significant differences, these observations certainly warrant further investigation in a larger prospective trial.

The sensitivity analysis suggests a low risk of bias due to combining all matched and unmatched pairs. Because of the small sample sizes and the relatively low number of cases with adverse neonatal outcomes, we were not able to determine the sensitivity, specificity, PPV, and NPV for preductal and postductal measurements separately. Further research in a larger sample size could validate whether separate models and predictive values should be conducted.

Calculation of the OSI does not require arterial blood sampling, and, thus, the OSI can be monitored continuously. These serial measurements might predict outcomes more reliably than incidental OI or OSI values. A retrospective cohort study already demonstrated that the *serial* OI had a better sensitivity and specificity than those in the lowest OI.[6] It is likely that changes in the trend of continuously measured OSI values could alert physicians at an early stage of clinical deterioration and, thus, the need for additional therapy. However, whether the OSI could replace the OI or

should rather be used as an additional tool in clinical decision-making needs further investigation.

Strengths of our study include the selective use of arterial blood samples and the pairing of OI and OSI values based on preductal or postductal measurements, which has not been described before. Due to the retrospective design, we could not always determine ventilator settings and respiratory parameters exactly at the time point of blood sampling. For the majority of data this was within seconds, and, thus, we believe that the impact of this was limited. Also, obtaining solely *matched* OI-OSI pairs was not always possible due to absence of the required SpO_2 value. High-frequency oscillation ventilation uses a higher MAP than conventional mechanical ventilation, thereby potentially falsely increasing the OI and OSI measurements.[19] But, as our local ventilation strategies in CDH only include conventional mechanical ventilation, we could not confirm this hypothesis. Furthermore, as we were limited by our sample size, we could not add additional factors to our model such as (fetal) haemoglobin levels and partial pressure of carbon dioxide, both of which potentially influence the oxygen dissociation curve.[18] Moreover, we recommend that OSI should be interpreted carefully if SpO_2 is >95%. To capture the most relevant data for early prediction, we only included measurements during the first 24 hours after birth. Extrapolation to the period thereafter seems reasonable as we believe that the relation between the OI and OSI does not differ after 24 hours.

CONCLUSION

Our data suggest that OSI measurements could replace OI measurements in infants with a CDH. In the first 24 hours after birth, the predictive values and discriminative ability of the OI and OSI are similar for pulmonary hypertension, ECMO therapy, and mortality. Continuously measured OSI values have the potential to offer a real-time guidance on therapy in clinical practice.

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Supplementary Table 1 Characteristics of data on preductal matched pairs and postductal matched pairs

	Preductal matched (n=245)	Postductal matched (n=73)
pH	7.25 [7.20-7.29]	7.27 [7.23-7.32]
PaO_2 (mmHg)	96.0 [63.8-137.3]	81.8 [54.0-119.3]
FiO_2 (%)	44 [35-100]	66 [45-91]
MAP (cmH2O)	12.6 [10.6-14.7]	12.4 [11.0-14.4]
SpO_2 (%)	97 [93-99]	96 [90-99]
Body temperature (°C)	37.0 [36.8-37.3]	37.1 [36.7-37.5]
Oxygenation index	4.9 [3.1-12.4]	7.5 [4.6-20.5]
Oxygen saturation index	6.6 [3.6-12.5]	8.6 [5.1-13.6]

Data are expressed as median [interquartile range]. PaO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; MAP: mean airway pressure; SpO_2: oxygen saturation.

Supplementary Table 2 Sensitivity analysis on subgroups

	Intercept		Oxygenation index		pH	
	ß	*p*	ß	*p*	ß	*p*
Preductal matched						
245 pairs	8.38	0.69	0.37	<0.001	-0.52	0.86
24 groups						
Postductal matched						
73 pairs	72.67	0.04	0.32	0.001	-9.27	0.05
7 groups						
Unmatched						
80 pairs	139.38	0.003	0.45	<0.001	-18.49	0.004
13 groups						

ß reflects the change in oxygen saturation index for a one-unit increase in the corresponding predicting variable (i.e. oxygenation index and pH).

11 The oxygen saturation index as early predictor of outcomes in congenital diaphragmatic hernia

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ABSTRACT

Objective: The aim of the study was to evaluate the oxygen saturation index (OSI) as an early predictor of clinical deterioration in infants with congenital diaphragmatic hernia (CDH).

Methods: A single-centre retrospective cohort study was conducted in consecutive infants with isolated CDH with continuous OSI measurements collected in the first 24 hours after birth between June 2017 and July 2021. Outcomes of interest were pulmonary hypertension, extracorporeal membrane oxygenation (ECMO) therapy, and mortality. We evaluated the discriminative values of the maximum OSI value and of mean OSI values with receiver operator characteristic (ROC) analysis and the area under the ROC curve.

Results: In 42 infants with 49473 OSI measurements, the median OSI was 5.0 (interquartile range 3.1–10.6). Twenty-seven infants developed pulmonary hypertension on a median of day 1 (1-1), of which 15 infants had an indication for ECMO therapy, and 6 infants died. Maximum OSI values were associated with pulmonary hypertension, ECMO therapy, and mortality. Mean OSI values had an acceptable discriminative ability for pulmonary hypertension and an excellent discriminative ability for ECMO therapy and mortality. Although OSI measurements were not always present in the first hours after birth, we determined discriminative cut-offs for mean OSI values already in these first hours for pulmonary hypertension, the need for ECMO therapy, and mortality.

Conclusions: Continuous OSI evaluation is a promising modality to identify those infants at highest risk for clinical deterioration already in the first hours after birth. This provides an opportunity to tailor postnatal management based on the individual patient's needs.

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a birth defect that is associated with postnatal cardiopulmonary insufficiency and pulmonary hypertension.[1,2] Consequently, affected infants commonly need mechanical ventilation, pulmonary vasodilators, and/or extracorporeal membrane oxygenation (ECMO) therapy. Around 30% of all affected infants do not survive.[3] Early identification of those infants at risk for a complicated postnatal course could alert physicians and refine individualised treatment strategies. Ideally, risk stratification is done within the first hours after birth as early clinical deterioration due to pulmonary hypertension is not uncommon, yet this is not feasible with most of the currently available prediction models.[4-6]

Given that the severity of lung disease (i.e. pulmonary hypoplasia and pulmonary hypertension) has the largest influence on postnatal outcomes, it is reasonable to revert to markers that are a composite of elements determining the efficiency of gas exchange within the lungs. Such markers are the oxygenation index (OI) and oxygen saturation index (OSI), based on partial pressure of oxygen (pO_2) and on oxygen saturation (SpO_2), respectively. Both indices combine oxygen delivery (defined by mean airway pressure [MAP] and fraction of inspired oxygen [FiO_2]) and oxygen diffusion (pO_2 or SpO_2) into a ratio.[7,8] As the OSI could be monitored *continuously* and *transcutaneously*, in contrast to the commonly used OI that requires blood sampling, the OSI might be used for real-time and bedside guidance during the crucial first hours of life. We have recently demonstrated that both the OI and OSI predict adverse outcomes in infants with CDH, but up until now, studies have focused on either the predictive value of OSI measurements at pre-specified time points or the comparability of paired OI and OSI measurements.[9-15] Hence, studies on the predictive value of continuous OSI measurements are scarce, especially in infants with CDH.[16]

In this study, we hypothesised that continuous OSI measurements in the first 24 hours after birth can discriminate which infants are at highest risk for a complicated postnatal course. The OSI's discriminative value was assessed for clinically relevant outcomes: pulmonary hypertension, ECMO therapy, and mortality.

METHODS

Study design

We conducted a single-centre retrospective cohort study at the Erasmus MC, University Medical Centre (Rotterdam, The Netherlands). Eligible cases were added to

an existing database that was used in a recent study.[14] All consecutive infants born with a prenatally detected isolated left-sided or right-sided CDH between June 2017 and July 2021 were included. We excluded infants with a diaphragmatic eventration, infants that were out-born, infants receiving palliative care immediately after birth, infants that deceased in the delivery room, infants with confirmed syndromes that would influence the postnatal course, and infants with less than 1 hour of OSI measurements. The research protocol was approved by the Local Medical Ethical Committee (MEC-2020-0563) and informed consent was waived.

Postnatal management

Local postnatal management is based on the CDH EURO Consortium Guideline that recommends, among others, to (1) adapt respiratory support to reach a preductal SpO_2 between 80% and 95% and a postductal SpO_2 >70%, and (2) consider ECMO therapy in infants with an OI ≥40 for at least 3 consecutive hours.[17]

Data collection

The following baseline characteristics were collected from clinical charts for each patient: prenatal observed to expected lung-to-head ratio (o/e LHR), side of the diaphragmatic defect (left or right), liver position (intra-abdominal or intrathoracic), gestational age at birth, birthweight, umbilical artery pH, age at surgical repair, occurrence of sepsis confirmed by a positive blood culture, number of days on mechanical ventilation, need for supplemental oxygen on day 28, and number of days of hospital admission. OSI values were calculated for the first 24 hours after birth (FiO_2 [%]*MAP [cmH_2O]/SpO_2 [%]) by combining FiO_2, MAP, and SpO_2 measurements.[8] The respiratory settings (i.e. FiO_2 and MAP) and physiological measurements (i.e. SpO_2) are locally stored each minute, however not synchronised, as these measurements are collected by different devices. Therefore, we pre-specified a maximum time difference of 120 seconds between respiratory settings and physiological measurements. In CDH infants, both the preductal and postductal SpO_2 are commonly collected, but we aimed at collecting *preductal* SpO_2 measurements. Based on historical cohorts, OSI >8 is highly discriminative in the assessment of respiratory failure severity and the OSI's value is generally equal to half of the OI's value.[8,13,18,19]

Outcomes of interest were the presence of pulmonary hypertension, defined as an estimated right ventricular systolic pressure to systolic blood pressure ratio of ≥2/3 on echocardiography that required therapy; the need for ECMO therapy, defined as a clinical decision for ECMO requirement irrespective of actual ECMO initiation; and all-cause mortality before hospital discharge.[20] For each infant, OSI measurements were excluded after the time point at which the particular outcome of interest was observed.

Statistical analysis

Normality of the data was checked with QQ-plots and density distributions combined with the Shapiro-Wilk test. Continuous variables were described using mean ± standard deviation in case of a normal distribution and median [interquartile range] in case of a non-normal distribution. Categorical data are reported as number (percentage).

For each infant, we collected (1) the mean OSI for the first 1, 2, 3, 6, 12, and 24 hours after birth; and (2) the maximum (worst) OSI measurement during the first 12 hours and 24 hours after birth. A receiver operator characteristic (ROC) analysis and the area under the receiver operator characteristic curve (AUROC) assessed the discriminative ability of these parameters for the above-mentioned outcomes of interest using the R package "cutpointr". Optimal cut-offs and corresponding sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with the Youden index, which gives equal weight to the sensitivity and the specificity and optimises the differentiating ability. Differences in maximum OSI measurement between infants with and without one of the outcomes of interest were assessed with the Mann-Whitney test. Due to measurement errors, our dataset contains outliers such as FiO_2 values <21%, whereas hypoxic ventilation in CDH infants is not performed in our centre. To assess the risk on bias by including all data in our analysis, we performed a sensitivity analysis in which FiO_2 values <21% were set to 21% and MAP values <4 cmH_2O were removed. Statistical analyses were performed using the computing environment R (R Core Team [2020], Vienna, Austria). *P*<0.05 was considered statistically significant for all tests.

RESULTS

Baseline characteristics

The total study population consisted of 42 infants with CDH with a median gestational age at birth of 38^{+1} [37^{+4}-38^{+3}] weeks. Five infants were diagnosed with minor genetic or additional anatomical abnormalities. The baseline characteristics of all patients are depicted in Table 1. A total of 49473 OSI measurements were collected with a median number per patient of 1258 [1064-1335]. Minimum and maximum values of the respective parameters were FiO_2 20.5-100%, MAP 0.1-28.9 cmH_2O, and SpO_2 13-100%. Median OSI was 5.0 [3.1-10.6], and the first OSI measurement was collected at 0.5 hours after birth. Figure 1 depicts the OSI measurements of one specific patient. The majority of infants (n=27, 64%) developed pulmonary hypertension after birth; in 22 cases, this presented within the first 24 hours. Seven of the infants with pulmonary hypertension required ECMO therapy already within the first 24 hours because of

therapy-resistant pulmonary hypertension. In one case, ECMO therapy was not initiated on parental request and palliative care was given instead. Eight infants required ECMO therapy after the first 24 hours, seven of them because of therapy-resistant pulmonary hypertension and one because of severe left-sided cardiac failure. Six infants (14%) died before hospital discharge.

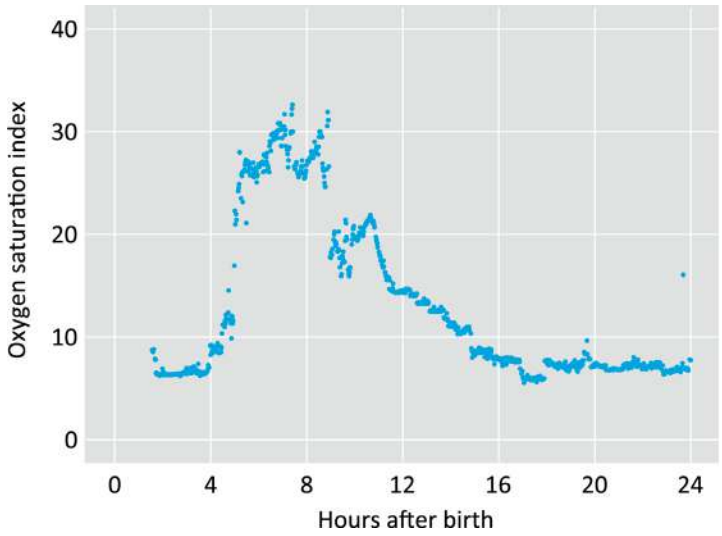

Figure 1 Oxygen saturation index over the first 24 hours for one patient with a left-sided diaphragmatic defect, an observed to expected lung-to-head ratio of 51%, and intra-abdominal liver position. This patient developed severe pulmonary hypertension on the first day, did not require extracorporeal membrane oxygenation, and survived until discharge.

Early prediction of adverse outcomes

The discriminative ability of the mean OSI was acceptable for the occurrence of pulmonary hypertension and excellent for ECMO therapy and mortality (Table 2). Optimal cut-offs, defined by highest sensitivity and specificity, for mean OSI values varied between 3 and 20 for the different time periods and outcomes. Already in the first hour after birth, mean OSI predicts outcomes: mean OSI ≥15 predicts both the occurrence of pulmonary hypertension (AUC 0.76; sensitivity 56%; specificity 100%; PPV 100%; NPV 56%) and need for ECMO therapy (AUC 0.96; sensitivity 83%; specificity 100%; PPV 100%; NPV 89%). Furthermore, mean OSI ≥17.3 predicts mortality (AUC 0.94; sensitivity 100%; specificity 91%; PPV 75%; NPV 100%).

Table 1 Baseline characteristics

	n	All subjects (n=42)
o/e LHR (%)	42	43.6 ± 12.7
Intrathoracic liver	42	20 (48)
Left-sided defect	42	36 (86)
Gestational age at birth (weeks^{+days})	42	38+1 [37+4-38+3]
Birthweight (g)	42	3000 [2725-3168]
Umbilical artery pH	39	7.29 [7.23-7.33]
Age at surgical repair (days)	40	5 [4-7]
Culture proven sepsis	42	13 (31)
Days on mechanical ventilation	42	10 [7-21]
Supplemental oxygen on day 28	37	19 (51)
Days of neonatal admission	42	35 [22-63]
Pulmonary hypertension	42	27 (64)
Age at onset pulmonary hypertension (days)	27	1 [1-1]
Need for ECMO therapy	42	15 (36)
Mortality	42	6 (14)
Age at mortality (days)	6	19 [7-21]

Data are expressed as mean ± standard deviation, median [interquartile range] or n (%).
o/e LHR: observed to expected lung-to-head ratio; ECMO: extracorporeal membrane oxygenation.

Maximum OSI

The maximum OSI values in the first 12 and 24 hours after birth were significantly higher in infants who developed pulmonary hypertension, required ECMO therapy, or died before discharge, as compared to those who did not (Figure 2). Also, the maximum OSI measurement was a reliable predictor for adverse outcomes. OSI ≥12.5 in the first 12 hours predicts the development of clinically relevant pulmonary hypertension (AUC 0.70; sensitivity 75%; specificity 67%; PPV 55%; NPV 83%). OSI ≥22 within the first 12 hours in infants with pulmonary hypertension predicts the need for ECMO therapy >12 hours (AUC 0.83; sensitivity 88%; specificity 83%; PPV 88%; NPV 83%). OSI ≥24 within the first 24 hours in infants with pulmonary hypertension predicts the need for ECMO therapy >24 hours (AUC 0.84; sensitivity 86%; specificity 88%; PPV 86%; NPV 88%). OSI ≥22 in the first 12 hours and 24 hours predicts mortality before discharge (AUC 0.85; sensitivity 100%; specificity 75-80%; PPV 40-46%; NPV 100%). In other words, all infants that died had an OSI measurement ≥22 within the first day and all infants with a maximum OSI measurement <22 survived.

Table 2 Prediction of adverse outcomes

		n	PH	n	ECMO	n	Mortality
Mean 0-1 hours	AUROC	14	0.76	14	0.96	14	0.94
	OSI cut-off		15.0		15.0		17.3
	Sensitivity		56%		83%		100%
	Specificity		100%		100%		91%
	PPV		100%		100%		75%
	NPV		56%		89%		100%
Mean 0-2 hours	AUROC	28	0.66	30	0.93	30	0.96
	OSI cut-off		9.1		13.8		20.0
	Sensitivity		38%		78%		100%
	Specificity		67%		100%		96%
	PPV		60%		100%		75%
	NPV		44%		91%		100%
Mean 0-3 hours	AUROC	27	0.68	33	0.93	33	0.96
	OSI cut-off		12.2		13.2		17.8
	Sensitivity		36%		80%		100%
	Specificity		100%		100%		93%
	PPV		100%		100%		67%
	NPV		59%		92%		100%
Mean 0-6 hours	AUROC	27	0.66	37	0.94	38	0.85
	OSI cut-off		3.5		12.5		14.9
	Sensitivity		100%		82%		80%
	Specificity		36%		96%		85%
	PPV		59%		90%		44%
	NPV		100%		93%		97%
Mean 0-12 hours	AUROC	23	0.64	37	0.92	41	0.89
	OSI cut-off		3.6		12.2		12.4
	Sensitivity		100%		90%		100%
	Specificity		33%		93%		80%
	PPV		44%		82%		46%
	NPV		100%		96%		100%
Mean 0-24 hours	AUROC	20	0.56	35	0.90	42	0.85
	OSI cut-off		3.2		9.9		8.6
	Sensitivity		100%		88%		100%
	Specificity		40%		93%		64%
	PPV		36%		78%		32%
	NPV		100%		96%		100%

AUROC: area under the receiver operator characteristics curve; ECMO: extracorporeal membrane oxygenation; OSI: oxygen saturation index; NPV: negative predictive value; PH: pulmonary hypertension; PPV: positive predictive value.

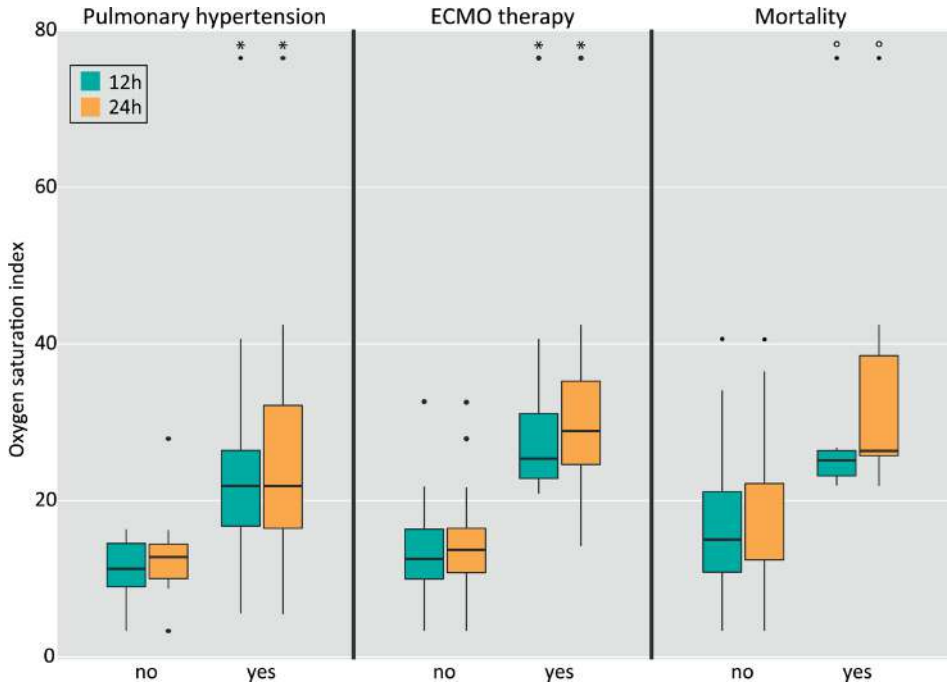

Figure 2 Maximum oxygen saturation index in the first 12 hours and 24 hours after birth. * $p<0.001$, ° $p<0.01$.

Sensitivity analysis

The sensitivity analysis did not show differences in the cut-off levels and corresponding sensitivity, specificity, PPV, NPV, and AUROC values for any of the combinations of mean OSI and adverse outcomes.

DISCUSSION

In this retrospective cohort study, we have assessed the predictive value of continuous OSI measurements for clinically relevant outcomes in infants born with an isolated CDH. Our results confirm that implementing continuous OSI evaluation may aid in the early prediction of pulmonary hypertension, need for ECMO therapy, and mortality. Hence, maximum and mean OSI values may be used to detect clinical deterioration at a very early stage.

Deterioration of a patient's cardiorespiratory status (e.g. pulmonary hypertension) often results in an increase in OSI – through intensified respiratory support and/or decreased SpO_2 – and consequently an increase in the mean of continuous OSI measure-

ments during a set period. Mean OSI is calculated during a set period of time; thus, it may be a better reflection of the patient's respiratory status than single measurements that can easily be influenced by outliers, such as maximum OSI. We confirmed that already in the first hour, reliable cut-offs for mean OSI could be established for all outcomes of interest. Only infants that developed pulmonary hypertension reached a mean OSI ≥15 in the first hour after birth. The same cut-off identifies infants at risk for ECMO therapy, with a specificity and PPV of 100%; this translates to all infants with a mean OSI ≥15 requiring ECMO therapy. Mean OSI in the first hour also proved to be a reliable marker to identify infants with a high risk of mortality: infants that ultimately survived to discharge had lower OSI values, and a corresponding mean value of <17.3 identified all survivors. As only 14 infants had OSI measurements in the first hour, our results have to be confirmed in a larger population.

We observed a decreasing trend in the established cut-offs for mean OSI values during the first 24 hours after birth. A potential explanation is the censoring of data by excluding infants that had already developed pulmonary hypertension or required ECMO therapy at a certain time point; those infants likely have the highest mean OSI values. Also, supportive therapy (e.g. fluid therapy or inotropic and vasopressor support) is often initiated during the first day of life, as cardiopulmonary problems regularly arise in these hours, potentially improving the infant's cardiorespiratory status and with that the OSI. Although the discriminative ability of mean OSI for pulmonary hypertension was still *acceptable*, it was not as good as the *excellent* discriminative ability for ECMO therapy and mortality. This might be the result of our retrospective study design and the challenge in determining the exact time point of developing pulmonary hypertension.

In our cohort, maximum OSI values in the first 12 and 24 hours were associated with all outcomes of interest and they reliably predicted these outcomes. Infants with any OSI value ≥12.5 are at high risk for the occurrence of pulmonary hypertension, and in these infants, additional or prophylactic therapies could be considered (e.g. pulmonary vasodilators). An OSI value ≥22 is strongly associated with both the need for ECMO therapy and mortality, both of which are in accordance with previous findings. We speculate that individualising and intensifying therapy in the OSI range between 12.5 and 22 might avoid further clinical deterioration.[14] However, more evaluation of this concept is warranted.

We have previously shown comparable predictive values of OSI values equivalent to the OI values that are currently used to decide on upscaling therapy such as ECMO.[12,14] However, the main advantage of continuous OSI measurements is that it may provide

early warnings of clinical deterioration, thus allowing for preventive measures rather than adjusting treatment at the moment that clinical deterioration has already occurred. Although we did not assess this, real-time OSI measurements may provide an opportunity to evaluate treatment effectiveness without the necessity of repeated blood sampling, for instance when pharmaceutically managing pulmonary hypertension, given the considerable individual variability in treatment response.

Another consideration is that ineffective ventilation, evaluated by partial pressure of carbon dioxide (CO_2), is equally as important as inadequate oxygenation when it comes to CDH-related mortality.[21-23] In that respect, recent advances in developing transcutaneous CO_2 monitoring devices are encouraging and combining this with OSI may provide a more complete evaluation of the infant's respiratory status and may potentially optimise our prediction model even further.

There has been growing interest in the association between markers of cardiac function and disease severity with consequent adverse outcomes in infants with CDH.[24] Markers such as left ventricular dysfunction, pro-b-type natriuretic peptide levels, lactate, and echocardiographic measures have been established as early predictors of outcomes.[24-29] Combining early cardiac markers with early markers of respiratory function, such as the OSI, might provide a more thorough prediction model that could identify a population at high risk for adverse outcomes. An advantage of this combination over currently used prediction models, such as the Brindle scoring model, Wilford Hall/Santa Rosa prediction model, and Score for Neonatal Acute Physiology-II, is the use of continuous measurements instead of either only the worst value in a set time period or binary outcomes at baseline.[4-6,22,30,31]

A limitation of using physiological data is the issue of measurement errors. In this study, we have deliberately not removed any outliers from the dataset to provide an accurate reflection of continuous OSI monitoring in day-to-day clinical practice. Anticipating on the development of monitoring equipment with algorithms that can filter between clinically valid and invalid values, we carried out a sensitivity analysis using a clean dataset. The sensitivity analysis did not show significant differences in the predictive capacity of the parameters that we have evaluated; consequently, data collected at the patient's bedside could be used without further data cleaning. Although we are confident to have collected mainly preductal SpO_2 measurements due to the standard of care in our centre, we acknowledge that our dataset might contain a limited number of postductal SpO_2 measurements, which we were unable to exclude due to the retrospective study design. Further evaluation of continuous OSI monitoring using solely preductal SpO_2 measurements could validate our results.

Another limitation is that SpO_2 is considered a suboptimal reflection of oxygenation when compared to pO_2, as its accuracy is relatively low and patients show a variable response on increasing FiO_2 levels.[32-35] As such, we do not recommend to replace OI measurements with OSI measurements at this stage, but we propose to add continuous OSI measurements as early indication of a complicated course.

We considered but did not use a combined outcome as main outcome, as the outcomes of interest are inherently associated with each other and may compete if mutually exclusive. However, all infants who died completed the triad of pulmonary hypertension, ECMO requirement, and mortality. Therefore, a combined outcome would not have increased the validity of our results. The high incidence of the main outcomes and availability of nearly 50000 OSI measurements allowed us to run multiple analyses and explore different time periods in a relatively small study population. We support validation of our findings in a larger multicentre cohort and expansion to lower risk patient groups. To make OSI values available in other centres, real-time OSI values, mean values, and maximum values need to be calculated, which are based on parameters (e.g. FiO_2, MAP, and SpO_2) that are readily available. Implementation in day-to-day practice of these non-invasive continuous OSI measurements requires confirmation of the clinical value of OSI as a real-time bedside measure in prospective clinical studies.

CONCLUSION

Continuous OSI measurements are a reliable predictor of outcomes in infants with CDH. We now propose continuous OSI evaluation as a promising modality allowing early identification of infants with CDH with the highest risk of developing pulmonary hypertension, needing ECMO therapy, or postnatal death. Already in the first hours after birth, continuous OSI measurements could provide the opportunity to adjust postnatal therapy to the individual patient's needs.

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PART IV

| Summary & Discussion |

12 Summary

SUMMARY

Congenital diaphragmatic hernia (CDH) is a birth defect that affects around 1 in 2500 live born infants and despite improvements in clinical care only around 70% of the infants survive to discharge. The main reason for mortality is the underlying lung disease, translating into respiratory insufficiency and pulmonary hypertension after birth. The research projects presented in this thesis focussed on specific aspects of perinatal care in infants with CDH.

GENERAL INTRODUCTION

In **chapter 1** we first provide a summary of recent developments in perinatal care and research in infants with CDH. **Chapter 1** also outlines the aims and scope of the research projects presented in this thesis. In the period before birth we focus on refining parental counselling in case of a prenatal diagnosis of CDH. Next, we present an overview of the cardiopulmonary changes occurring during the transition from fetus to neonate and of potential improvements in current perinatal care. In the period after birth, we focus on promising markers to individualise postnatal care for each infant with CDH.

PART I | BEFORE BIRTH

Chapter 2 describes a single-centre cohort including all prenatally diagnosed CDH cases in more than a decade. Around one fourth of all parents terminated the pregnancy and factors that were associated with this decision were solely fetal factors, namely disease severity and presence of additional abnormalities, and not parental factors. The disease severity of fetuses with CDH is estimated based on the observed to expected lung-to-head ratio (o/e LHR) determined with ultrasound, the position of the liver, and the side of the defect. As the estimation of fetal lung size is prone to measurement errors, counselling of parents should preferentially be carried out in specialised centres with experience in both prenatal and postnatal care for infants with CDH.

The use of the above-mentioned prenatal imaging markers has been evaluated in cohorts that mainly consist of term born infants. **Chapter 3** describes a multicentre retrospective cohort study on the association between prenatal ultrasound markers and survival in infants with CDH born ≤32 weeks of gestation. We demonstrated that

fetal lung size was also associated with survival in preterm born infants not receiving fetoscopic endoluminal tracheal occlusion (FETO) therapy. Moreover, the negative effects of prematurity were more pronounced in infants with left-sided CDH and estimated severe lung hypoplasia. FETO therapy seemed to have a positive effect on survival in left-sided CDH, despite a shorter tracheal occlusion time and preterm birth.

PART II | AT BIRTH

The transition from fetus to neonate is a highly complicated event during which many cardiorespiratory physiological changes must occur to guarantee adequate gas exchange. Knowledge of the potential negative impact of immediate cord clamping on the fetal-to-neonatal transition is translated into many guidelines advising to delay cord clamping up to three minutes. Still, obstetricians are especially hesitant to delay cord clamping for longer than one minute during a caesarean section because of the potential risk of increased maternal blood loss. In the study shown in **chapter 4**, we reassuringly demonstrated that the incidence of maternal bleeding complications did not change after implementation of delayed cord clamping for three minutes during caesarean sections. This provides guidance for centres that are working towards an optimised fetal-to-neonatal transition.

Infants with a complicated fetal-to-neonatal transition are often excluded from delayed cord clamping guidelines because of their need for additional support, an example being infants with CDH. Due to the underlying pathophysiology, infants with CDH might actually experience a significant negative impact of immediate cord clamping. Based on data from animal experiments, we foresee a more gradual fetal-to-neonatal transition if cord clamping is delayed until adequate lung aeration has been established, so-called physiological-based cord clamping (PBCC). In **chapter 5**, we present the trial protocol of the randomised multicentre PinC trial evaluating the effects of PBCC for infants with an isolated left-sided CDH on the incidence of pulmonary hypertension in the first 24 hours after birth.

International guidelines on delivery room management advise to routinely intubate all infants born with CDH immediately after birth. Considering the potential negative effects, immediate intubation may be too aggressive for the subgroup with a relatively mild degree of pulmonary hypoplasia. In December 2014, the Erasmus MC implemented a trial of spontaneous breathing for infants with isolated left-sided CDH, o/e LHR ≥50%, and intra-abdominal liver position. The data illustrated in **chapter 6**

indicate that 60% of the eligible infants still required intubation in the first hours after birth, but delayed intubation was not associated with adverse outcomes. Interestingly, infants that were spontaneously breathing required oxygen for shorter periods and were discharged home earlier. The results of this study both justified and warranted further evaluation of this approach, especially in the form of standardisation. In **chapter 7** we discuss a proposal for a spontaneous breathing approach algorithm developed in collaboration with international experts on CDH, neonatal resuscitation, and fetal physiology. In this algorithm we implemented the initiation of non-invasive respiratory support to assist the fetal-to-neonatal transition. With continuous evaluation of the infant's respiratory state, respiratory support can be titrated individually.

A challenge inherent to current delivery room guidelines in infants with CDH is how to reach adequate sedation prior to intubation. Although the negative effects of awake intubation are well-known, current guidelines result in most infants with CDH being intubated without prior sedation. **Chapter 8** depicts the results of an international survey on pre-intubation sedation and, despite a general emphasis on the need to improve current pain and stress management in the delivery room, premedication is used in only 19% of the responding centres. Other than that, we identified a substantial variation in the choice of drug and method of administration.

PART III | AFTER BIRTH

Infants with pulmonary hypertension secondary to CDH often fail to respond adequately to pulmonary vasodilators aiming at reducing pulmonary vascular resistance. Alterations in the pulmonary vasculature could explain the inadequate response to medication, but studying these alterations requires a lung biopsy. In **chapter 9** we evaluated our hypothesis that fetoplacental vessels could be used as an alternative since both vascular beds are exposed to the same circulating factors in the fetal circulation and both respond similarly to certain stimuli. Our data demonstrated that CDH fetoplacental arteries exhibit specific alterations that correspond with currently described alterations in CDH pulmonary vessels. For example, we found attenuated vasodilation through the nitric oxide-cyclic guanylate monophosphate pathway, which mimics the insufficient response of pulmonary vessels to nitric oxide. The fetoplacental arteries could thus be used as an innovative tool towards individualised care for infants with pulmonary hypertension, not just those with CDH.

Early postnatal identification of infants with CDH at risk for a complicated postnatal course could alert physicians and enable early individualised therapy. Despite avail-

able prediction models, risk stratification in the first hours after birth is challenging. Early markers of the respiratory status seem promising as the severity of lung disease is a main contributor to adverse outcomes. An example is the oxygenation index, a ratio that combines oxygen delivery (i.e. mean airway pressure and fraction of inspired oxygen) with oxygen diffusion (i.e. partial arterial pressure of oxygen). The oxygen saturation index is an alternative that uses the oxygen saturation instead of the partial arterial pressure of oxygen. In **chapter 10** we confirmed that oxygenation index and oxygen saturation index are strongly correlated in infants with CDH in the first 24 hours after birth, and that the predictive value for adverse outcomes is not different. In **chapter 11** we demonstrated that already in the first hours after birth, continuous oxygen saturation index measurements provide an opportunity to identify which infants with CDH have the highest risk of clinical deterioration. We foresee a great benefit of using the oxygen saturation index as it allows for further individualised treatment strategies and early referral to expertise centres in healthcare systems in which postnatal care is not centralised.

13 Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Een congenitale hernia diafragmatica (in het Engels: **congenital diaphragmatic hernia**, CDH) is een zeldzame aangeboren aandoening die bij ongeveer 1 op de 2500 levend geborenen voorkomt. Bij deze kinderen zit er een gat (**hernia**) in het middenrif (**diafragma**), waar buikorganen zoals maag, darmen en lever zich doorheen kunnen verplaatsen naar de borstholte. De longen hebben daardoor niet voldoende ruimte en dit is één van de redenen voor een verstoorde ontwikkeling van de longen, zogenaamde **long hypoplasie**. Gedurende de zwangerschap worden de longen nog niet gebruikt en zorgt de moederkoek (**placenta**) voor gasuitwisseling, oftewel aanvoer van zuurstof en afvoer van koolzuurgas. Na de geboorte komen deze kinderen vaak in de problemen omdat ze minder goed in staat zijn zuurstof op te nemen (**respiratoire insufficiëntie**) en de bloedvaten van de longen niet voldoende open gaan staan, wat leidt tot een te hoge bloeddruk in te longen (**pulmonale hypertensie**). Ondanks verbeteringen in de zorg overleeft slechts 70% van deze kinderen tot ontslag uit het ziekenhuis. Dit proefschrift richt zich op specifieke aspecten in de zorg rondom geboorte (**perinatale zorg**) voor kinderen met CDH.

ALGEMENE INLEIDING

In ***hoofdstuk 1*** wordt een samenvatting gegeven van recente ontwikkelingen in de perinatale zorg en in onderzoek bij kinderen met CDH. Dit hoofdstuk beschrijft ook de doelstellingen van dit proefschrift. In de periode voor de geboorte (**prenataal**) richten we ons op het verfijnen van de voorlichting aan ouders (**counseling**) bij een diagnose van CDH. Vervolgens geven we een overzicht van de veranderingen die optreden in het hart, de longen en de bloedsomloop tijdens de overgang van foetus in de baarmoeder naar pasgeborene buiten de baarmoeder. Ook geven we een overzicht van de huidige zorg en mogelijke verbeteringen. In de periode na geboorte (**postnataal**) richten we ons op veelbelovende markers die kunnen helpen de zorg aan te passen aan elk individueel kind met CDH.

DEEL I | VOOR GEBOORTE

In ongeveer 70% van de gevallen wordt CDH voor de geboorte ontdekt. Dit geeft ouders de keuze om de zwangerschap uit te dragen of af te breken. In ***hoofdstuk 2*** beschrijven we een onderzoek naar alle gevallen van CDH die voor geboorte ontdekt werden in een periode van meer dan tien jaar. Ongeveer een kwart van alle ouders

beëindigde de zwangerschap. De geschatte ziekte ernst en de aanwezigheid van andere aangeboren afwijkingen waren geassocieerd met deze keuze. Bij ongeboren baby's met CDH wordt de ziekte ernst geschat op basis van de verhouding tussen de grootte van de longen en de hoofdomtrek (**lung-to-head ratio**, LHR) die beide worden bepaald op echobeelden. De LHR wordt vervolgens uitgedrukt als een percentage van wat bij een gezonde baby verwacht wordt, gecorrigeerd voor de zwangerschapsduur op het moment van de echo (observed to expected, **o/e LHR**). Daarnaast wordt gekeken naar de positie van de lever (in de buik/**intra-abdominaal** of in de borstholte/**intrathoracaal**) en de kant van de middenrif breuk (**linkszijdig** of **rechtszijdig**). Op basis van deze factoren wordt de **ziekte ernst** geschat: **milde**, **matige** of **ernstige** long hypoplasie. Aangezien het meten van de grootte van de longen gevoelig is voor meetfouten, gebeurt dit bij voorkeur in een ziekenhuis met uitgebreide ervaring. Om ouders de juiste informatie te geven over de ziekte ernst van hun ongeboren baby moeten zij dus worden verwezen naar een gespecialiseerd ziekenhuis.

De factoren die vóór geboorte gebruikt worden om de ziekte ernst in te schatten zijn met name onderzocht in kinderen die voldragen waren bij geboorte. In ***hoofdstuk 3*** hebben we gekeken of we deze factoren ook kunnen gebruiken bij kinderen met CDH die worden geboren vóór 32 weken zwangerschapsduur (**ernstig prematuur**). Uit gegevens die in zeven internationale ziekenhuizen verzameld werden, bleek dat de longgrootte ook bij ernstig prematuur geboren kinderen met CDH een verband heeft met overleving. Dit was alleen zo in de groep kinderen met linkszijdige CDH die geen operatie hebben ondergaan tijdens de zwangerschap. Deze operatie heet **FETO** (foetoscopische endoluminale tracheale occlusie). Hierbij wordt tijdens de zwangerschap met een kijkoperatie (**foetoscopisch**) een ballonnetje geplaatst in de luchtpijp van de baby (**tracheale occlusie**) ter bevordering van de ontwikkeling van de longen. In ons onderzoek leek FETO therapie te zorgen voor een vergrote kans op overleving bij kinderen met linkszijdige CDH, ondanks kortere occlusietijd van de luchtpijp en vroeggeboorte. Ten slotte zagen we dat de effecten van vroeggeboorte het meest uitgesproken waren in kinderen met linkszijdige CDH en geschatte ernstige long hypoplasie, dus met zeer kleine longen.

DEEL II | BIJ GEBOORTE

Bij geboorte moeten het hart, de longen en de bloedsomloop zich in hele korte tijd aanpassen aan de situatie buiten de baarmoeder, want de gasuitwisseling die eerst in de placenta plaatsvond moet in de longen gaan plaatsvinden. Inmiddels is bekend dat het nadelig is voor het kind om de navelstreng direct na geboorte af te klemmen

en daarom adviseren veel richtlijnen om dit pas drie minuten na geboorte te doen. Toch is men vaak huiverig om bij een keizersnede langer dan één minuut te wachten vanwege het risico op bloedverlies bij de moeder. In ***hoofdstuk 4*** beschrijven we een onderzoek dat laat zien dat de hoeveelheid bloedverlies bij moeders niet toenam toen de navelstreng pas na drie minuten werd afgeklemd na een keizersnede in plaats van direct na de geboorte.

Bij pasgeborenen die problemen ervaren in de overgang van binnen de baarmoeder naar buiten de baarmoeder (**foetale-neonatale-transitie**) wordt de navelstreng vaak direct afgeklemd aangezien ze ondersteuning nodig hebben na geboorte. Dit is ook het geval bij kinderen met CDH. Vanwege de longproblemen bij deze kinderen kunnen juist zij veel negatieve effecten ervaren van het direct afklemmen van de navelstreng. Op basis van gegevens uit dierexperimenten verwachten wij een betere foetale-neonatale-transitie wanneer de navelstreng pas wordt afgeklemd zodra de longen luchthoudend zijn. Dit noemt men fysiologisch afnavelen (in het Engels: physiological-based cord clamping, **PBCC**). In ***hoofdstuk 5*** presenteren we het protocol voor het **PinC** onderzoek dat kijkt naar de effecten van PBCC op het ontstaan van pulmonale hypertensie binnen de eerste 24 uur na geboorte bij pasgeborenen met linkszijdige CDH. Dit onderzoek wordt uitgevoerd in meerdere centra wereldwijd.

Internationale richtlijnen adviseren om alle pasgeborenen met CDH direct te **intuberen** na geboorte, wat betekent dat een buisje in de luchtpijp wordt geplaatst en een machine via deze buis de ademhaling overneemt. Dit heeft helaas ook negatieve effecten en mogelijk is intubatie te agressief voor kinderen met relatief milde long hypoplasie. In het Erasmus MC is men in december 2014 gestart kinderen met linkszijdige CDH, o/e LHR ≥50% en intra-abdominale leverpositie zelf te laten ademhalen in plaats van te intuberen (in het Engels: **spontaneous breathing approach**). Het onderzoek beschreven in ***hoofdstuk 6*** laat zien dat 60% van deze kinderen alsnog geïntubeerd werd in de eerste uren na geboorte, maar deze uitgestelde intubatie zorgde niet voor slechtere uitkomsten. Kinderen die spontaan ademhaalden hadden minder dagen zuurstof nodig en konden eerder worden ontslagen. Deze resultaten lieten zien dat het nodig was om deze aanpak verder te verbeteren. Dit hebben we gedaan in samenwerking met internationale experts op het gebied van CDH en de foetale-neonatale-transitie. In ***hoofdstuk 7*** bespreken we een voorstel voor een protocol voor spontane ademhaling na geboorte in plaats van intubatie. In dit protocol wordt aangeraden te starten met **niet-invasieve ademhalingsondersteuning**. Hierbij haalt het kind zelf adem en krijgt hij/zij ondersteuning in de vorm van extra zuurstof en/of extra druk om de luchtwegen open te houden. De ondersteuning kan vervolgens aangepast worden aan de hand van hoeveel moeite het kind heeft met de ademhaling.

Als kinderen met CDH wel geïntubeerd worden, is het vaak moeilijk om voorafgaand hieraan medicatie te geven die zorgt voor een verdovend effect (**sedatie**). Kinderen met CDH worden daarom vaak ‘wakker’ geïntubeerd terwijl dit kan zorgen voor negatieve effecten zoals pijn en stress. In ***hoofdstuk 8*** beschrijven we de resultaten van een internationale enquête over het gebruik van sedatie vóór intubatie. Deze resultaten laten zien dat slechts in 19% van alle ziekenhuizen sedatie wordt gegeven voorafgaand aan intubatie, terwijl veel respondenten benadrukken dat pijn en stress verminderd moeten worden bij deze kinderen. Bovendien gebruiken ziekenhuizen verschillende medicatie en zien ze hier wisselende effecten van. Een standaard protocol voor medicatie vóór intubatie zou de zorg kunnen verbeteren.

DEEL III | NA GEBOORTE

Kinderen met pulmonale hypertensie als gevolg van CDH reageren vaak onvoldoende op medicijnen die gegeven worden om de longvaten te openen, waardoor een hoge weerstand in de longvaten blijft bestaan. Dit kan verklaard worden door veranderingen in de longvaten, maar de longvaten kunnen alleen bestudeerd worden door een stukje longweefsel te verwijderen (**biopsie**). In ***hoofdstuk 9*** hebben wij onderzocht of de bloedvaten uit de placenta (**foetoplacentale vaten**) als alternatief gebruikt zouden kunnen worden. Dit idee is gebaseerd op het feit dat foetoplacentale vaten en longvaten allebei onderdeel zijn van de bloedsomloop van een ongeboren baby en dus zijn blootgesteld aan dezelfde stoffen in het bloed. Ook reageren deze bloedvaten vergelijkbaar op bepaalde prikkels. Wij toonden specifieke veranderingen aan in de foetoplacentale vaten bij CDH, die overeenkomen met al beschreven veranderingen in longvaten bij CDH en die de ontoereikende reactie op medicijnen mogelijk kunnen verklaren. Meer onderzoek van de foetoplacentale vaten zou dus een innovatieve manier kunnen zijn om de zorg voor kinderen met pulmonale hypertensie te verbeteren.

Aangezien de ziekte ernst verschilt per kind met CDH, lopen deze kinderen ook in verschillende mate een risico op problemen na geboorte. Als men al vroeg na geboorte zou kunnen bepalen welke kinderen het hoogste risico hebben op complicaties, zouden artsen al vroegtijdig kunnen starten met therapie aangepast aan het kind (**geïndividualiseerde zorg**). Met de huidige beschikbare voorspellingsmodellen is het moeilijk om dit risico in de eerste uren na geboorte vast te stellen. De ernst van de longziekte levert een belangrijke bijdrage aan het ziektebeloop en dus lijkt het veelbelovend om naar markers te kijken die hier een inschatting van geven. Een voorbeeld is de **oxygenation index** die een verhouding weergeeft van hoeveel zuurstof het kind krijgt en hoeveel zuurstof daadwerkelijk in het bloed belandt. Een alternatief is de

oxygen saturation index en het voordeel hiervan is dat geen bloedmonster nodig is om de hoeveelheid zuurstof in het bloed te bepalen, omdat gebruik wordt gemaakt van een sensor op de huid. In ***hoofdstuk 10*** hebben wij bevestigd dat de oxygenation index en de oxygen saturation index een sterk verband hebben in de eerste 24 uur na geboorte bij kinderen met CDH. Ook zagen we dat deze twee metingen even goed waren in het voorspellen van problemen na geboorte. In ***hoofdstuk 11*** hebben we vervolgens aangetoond dat continue metingen van de oxygen saturation index al in de eerste uren na geboorte kunnen helpen om te bepalen welke kinderen met CDH het hoogste risico hebben op problemen. Wij verwachten dat deze continue metingen kunnen helpen de zorg af te stemmen op de noden van elk individueel kind met CDH. Ook kunnen deze metingen helpen om te bepalen wie eventueel naar expertise ziekenhuizen moet worden doorverwezen voor meer intensieve behandeling.

14 General discussion

GENERAL DISCUSSION AND PERSPECTIVES

A congenital diaphragmatic hernia (CDH) is a rare birth defect characterised by incomplete closure of the diaphragm. After birth, CDH is associated with significant neonatal morbidity and mortality due to a combination of pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction.[1-3] Despite improvements in clinical care, around 30% of these infants do not survive.[4-6] The research projects reported in this thesis provide a critical appraisal of important aspects of perinatal care for infants with CDH. This chapter summarises the main findings, limitations, and future research recommendations.

PART I | BEFORE BIRTH

In the period before birth we focussed on refining parental counselling by evaluating which factors are important for parents. Earlier studies have already reported that both disease-related factors (e.g. disease severity) and parental demographic factors (e.g. ethnicity) play a role for parents when deciding to continue or terminate a pregnancy complicated by prenatal diagnosis of a fetal abnormality.[7-15] In our single-centre cohort including all pregnancies with the prenatal diagnosis of CDH, a fourth of all parents terminated the pregnancy and only disease-related factors were associated with this decision.[16] Specifically, the expected severity of pulmonary hypoplasia and the presence of additional fetal abnormalities were associated with the parental decision.[16] To refine and to ensure accurate counselling, it is essential to avoid speculation about disease severity and to refer parents to specialised centres that have expertise in prenatal, perinatal, and postnatal CDH-care.[17,18] The multidisciplinary expertise of maternal-fetal medicine specialists, neonatologists, and paediatric surgeons guarantees that parents receive complete information on both disease severity and the consequent postnatal prognosis.[17] Discordant viewpoints should however be avoided as these can be very distressing for parents and it could therefore be encouraged to limit parental counselling to a fixed group of multidisciplinary clinicians.[17]

The presence of additional fetal abnormalities thus contributes to the parental decision, but a challenging part of counselling is the occasional finding of genetic variations with unknown clinical significance.[16] In fact, the incidence of these variations is expected to increase with the introduction of more extensive genetic testing such as whole exome sequencing.[19-21] Prior to genetic testing, the preferred approach to reporting genetic abnormalities with unknown or no clinical significance should be discussed with parents.[21] Other than that, the 13-week structural ultrasound exami-

nation can introduce a period of uncertainty for parents as adequate prediction of postnatal prognosis is difficult this early in gestation. However, the true impact of this 13-week ultrasound is yet to be determined.

In contrast to earlier studies we did not observe an association between parental demographic factors, such as ethnicity or socioeconomic background, and the decision to terminate the pregnancy.[15,16] Our study was however limited by its retrospective single-centre design and the number of missing data; thus, the importance of parental factors should not be ruled out.[16] Although questionnaires could inform us on the exact parental decision process, one could certainly argue that data collection is time consuming and at risk of recall bias and selection bias, with parents who continued the pregnancy being more likely to respond. In addition, results from studies in other diseases already provide a direction for counselling in prenatal CDH. Despite some conflicting outcomes, the observed trend is that non-Caucasian women with lower levels of education and a younger age are less likely to terminate the pregnancy.[9,15] Although we can only speculate on underlying reasons, it could be that the information provided during counselling is too complicated.[15] Clinicians should thus take these factors into account and adjust counselling accordingly. Additionally, standardised documentation of which factors play a role for parents in the decision process is encouraged to enable future evaluation.

Research in infants with CDH can be complicated by the heterogeneity of the population caused by laterality of the defect, defect size, fetal surgery, and gestational age at birth.[22,23] Adjusting statistical analyses for each factor often results in too small sample sizes per subgroup and a lack of significance. Parental counselling in subgroups, such as cases with right-sided CDH or very preterm born CDH cases, can therefore be difficult. Aiming at refining parental counselling in the latter subgroup, we evaluated the association between prenatal predictors and survival in infants with CDH born ≤32 weeks of gestation in a multicentre study.[24] Although fetal lung size was associated with survival in infants with left-sided CDH managed expectantly during pregnancy, it was not possible to define cut-off values for lung size that apply to this subgroup of infants born very preterm.[24-26] In addition, the number of infants with right-sided CDH was too low to draw firm conclusions despite data collection in seven high-volume centres. Larger cohorts are thus required to determine the exact predictive value of fetal lung size in this subgroup, but we emphasise that collecting larger databases is challenging, especially for right-sided CDH. By now it has become clear that right-sided CDH should be considered as a separate entity, but because of its rareness we have to rely on results from observational studies in guiding clinical practice.[25,27,28] The use of international registries might therefore be interesting.

Evaluation of other parameters of interest, such as stomach position and percentage of liver herniation on MRI, in specific subgroups also requires larger databases.[29-36]

The future: refined parental counselling

When a prenatal diagnosis of CDH is made, the parents are promptly referred to a centre with expertise in caring for infants with CDH, and they are given the option to perform additional anatomical and genetic testing. In a way that is comprehensible for the parents, a clinician discusses the results and their clinical significance. Optimised and individualised prediction models, based on fetal characteristics, provide parents with an accurate estimation of disease severity and postnatal prognosis of their infant. These prediction models can also be used in specific subgroups, such as fetuses with right-sided CDH, fetuses facing imminent very preterm birth, or fetuses that underwent fetal surgery. This information helps parents make an informed decision about whether to continue the pregnancy or terminate it.

PART II | AT BIRTH

The fetal-to-neonatal transition encompasses many physiological changes and infants with CDH often face a complicated transition due to pulmonary hypoplasia and cardiac dysfunction. Routine management after birth includes several interventions aiming at guaranteeing the best possible start of neonatal life, but remarkably most interventions are largely eminence-based rather than evidence-based, and most are not tailored to the individual infant's disease severity.[37] We challenge the status quo and argue that current routine care at birth should be reconsidered towards evidence-based and individualised care for each infant with CDH.

Current routine care at birth for infants with CDH

The umbilical cord is clamped immediately after birth, after which the infant is transferred to the resuscitation table and intubation is performed. Mechanical ventilation is started, following the CDH EURO Guidelines; settings are titrated based on the infant's physiology reflected by factors such as heart rate and saturation.[37] Given the priority of securing the airway and initiating respiratory support, intravenous access is usually obtained afterwards. Medications such as sedative drugs, analgesics, and muscle relaxants are administered. Finally, a nasogastric/orogastric tube with continuous suctioning is positioned. The infant is then transferred to the intensive care unit.

Umbilical cord clamping

Despite ample evidence on the neonatal benefits of delaying umbilical cord clamping, most infants with CDH still have their cords clamped within the first minute in anticipation of the immediate need for respiratory support to avoid hypoxia.[38-48] Conversely, these infants could actually benefit most from prolonged placental support as they often face a complicated transition due to the underlying disease.[2,3,43,49,50] In each infant, cord clamping results in a decrease in left ventricular preload, due to loss of the umbilical venous return via the ductus venosus, in combination with an increase in systemic vascular resistance.[43,51] Immediate aeration of the lungs reduces the negative effects on the cardiac output by causing an increase in pulmonary blood flow thereby both re-establishing left ventricular preload and reducing the increase in afterload.[51] In contrast to healthy infants, infants with CDH often have pulmonary hypoplasia and left ventricular hypoplasia and dysfunction, which can cause delayed lung aeration and a prolonged period of reduced cardiac output.[2,43,50]

Two multicentre trials are currently evaluating the effects of physiological-based cord clamping (PBCC) on outcomes in infants with CDH, being the PinC trial and the CHIC trial.[52,53] In PBCC the umbilical cord is only clamped after the lungs have taken over the placental function, meaning that the lungs have been aerated. It is however challenging to determine when exactly the lungs have aerated. In both trials, cord clamping is therefore guided by available physiological data that are considered good proxies, such as heart rate, oxygen saturation, and level of oxygen supplementation.[52-54] Adequate lung aeration could be ascertained with novel modalities such as evaluation of ductus arteriosus flow on echocardiography, lung ultrasound, and tidal volumes; however, further research is warranted as technical limitations or logistic feasibility complicate implementation.[55,56] Although a set moment to clamp the cord does not seem right as differences in the underlying disease severity ask for an individualised approach, a maximum time to delay umbilical cord clamping of ten minutes is mandated by protocol in the PinC trial.[53] This is because of the risk of maternal bleeding complications, but lung aeration might still be ongoing at that moment thereby potentially mitigating the actual benefits of PBCC.[53,57,58]

In the PinC trial, the primary outcome is the occurrence of pulmonary hypertension within the first 24 hours and a relative risk of one-third is considered clinically relevant.[53] Although the gold standard to diagnose pulmonary hypertension is measurement of the pulmonary arterial pressure via right heart catheterisation,[59] CDH-related pulmonary hypertension CDH is traditionally defined as echocardiographic measurement of elevated right-heart pressures relative to systemic blood pressure.[60] This definition likely overestimates the incidence of clinically relevant

pulmonary hypertension as treatment is often not started in absence of clinical signs, but defining pulmonary hypertension based on solely clinical signs might be too subjective. As such, a combination of clinical and echocardiographic parameters would provide a more accurate definition. In the CoDiNOS trial and the PinC trial, pulmonary hypertension is defined as the presence of at least two out of four criteria, of which two clinical and two echocardiographic criteria.[53,61] This definition probably still overestimates the incidence of clinically relevant pulmonary hypertension with only two criteria being required.[53,61] The lack of a consensus definition also has a negative impact on the ability to compare research findings from different studies. A consensus definition is thus crucial and highly anticipated, as it can be considered one of the most important knowledge gaps that needs to be addressed.[3]

The PinC trial started in the Erasmus MC in May 2020 and by now, four international centres have joined the trial. Unfortunately, the inclusion rate is lower than was anticipated on and the main reason for this is a delay in trial initiation in international centres. Despite an early focus on recruiting centres and the interest of many international centres, significant delays have been encountered in gaining local ethical approval, organising local insurances, and reaching legal approval on a clinical trial agreement. As such we emphasise that European and international regulations should be changed to facilitate rather than to obstruct implementation of clinical trials in interested international centres. With an inclusion rate of over 85% of all eligible patients in the PinC trial, addition of currently interested high-volume centres will result in reaching the predefined sample size.

Although the trial results are only anticipated in the next years, we can already discuss the potential outcomes. If PBCC results in significantly worse outcomes compared to immediate cord clamping, the standard of care with immediate cord clamping should not be changed. If PBCC has a significant benefit over immediate cord clamping, PBCC should be implemented in clinical practice. It could also be the case that PBCC only improves outcomes in infants with estimated mild pulmonary hypoplasia, and not in infants with estimated moderate or severe pulmonary hypoplasia. In that case or if no significant differences between groups are demonstrated, implementation of PBCC could still be encouraged although it should then be discussed with both parents and clinicians. A reason to still implement PBCC in clinical practice is the possibility of interaction between parents and infant, which is especially meaningful in those infants quickly transferred to the intensive care unit for an often lengthy admission. Additionally, despite methodological differences, a meta-analysis using individual patient data from both trials on PBCC could strengthen the scientific evidence.[52,53]

International implementation of PBCC in combination with prospective data collection could have been an interesting alternative to a randomised controlled trial (RCT). On the other hand, simple implementation of PBCC would have resulted in a loss of the still existing equipoise, in which the benefits of PBCC have not yet been demonstrated in clinical trials. We can therefore not entirely discard the necessity of an RCT that eliminates the influence of selection bias and reduces confounding factors.[62,63] Regardless of the results, we envision that performing studies such as the PinC or the CHIC trial will not only guide routine care in the delivery room for infants with CDH, but also for other infants facing a complicated transition.

Initial respiratory support

Hypoxia is a known cause of pulmonary hypertension and to avoid this, infants with CDH receive respiratory support after birth.[64] International guidelines recommend immediate intubation to provide the required respiratory support after birth despite the lack of supporting data for this approach.[37,65] In fact, the European and Canadian guidelines both acknowledge that this recommendation is based on expert opinion.[37,65] The same is true for the concerns for gastro-intestinal distension impairing lung expansion when initiating non-invasive respiratory support.[37,65-67] Interestingly, the combination of immediate cord clamping and intubation complicated by tracheal deviation results in oxygen deprivation for several minutes – the exact problem current guidelines attempt to avoid. Yet, the unfounded dogma of compulsory primary intubation hampers evaluation of other approaches like non-invasive respiratory support. This in turn contributes to our lack of understanding whether the neonatal transition in CDH is best supported by supplemental oxygen and/or distending airway pressures.[67] We hypothesise that vigorous infants with CDH can initiate their transition without invasive ventilation and that initial oxygen deprivation could be avoided by a combination of PBCC and non-invasive respiratory support with high flow or continuous positive airway pressure (CPAP).

The recently developed algorithm for a spontaneous breathing approach in infants with expected mild pulmonary hypoplasia is a first step in the implementation of non-invasive respiratory support at birth.[68] Following this algorithm, infants are not intubated after birth but instead receive high flow or CPAP combined with early insertion of a nasogastric/orogastric tube.[68] This protocol was drafted after our small single-centre study had demonstrated that a spontaneous breathing approach resulted in earlier discharge from the intensive care unit, whereas an unsuccessful trial of spontaneous breathing did not appear to impact survival or short-term morbidity.[69] We acknowledge that an RCT could have revealed the true benefit of this approach, but the very limited number of eligible patients in combination with

the lack of equipoise in centres that had already implemented this approach posed a challenge. Instead, we opted for prospective collection of data on consecutive infants who were allowed an attempt of spontaneous breathing within the framework of an international research consortium: the VeSBA consortium.[68] We expect these data to contribute to our knowledge on how to best support each individual infants with CDH-related pulmonary hypoplasia during its transition period. As such, these data will be used to indicate future research directions and to consider implementation of initial non-invasive respiratory support in the larger group of infants with CDH.[68,69]

Immediate initiation of non-invasive respiratory support also creates a time window in which sedation can be administered prior to intubation, thereby avoiding awake intubation. Avoidance of stress and pain is of specific interest for infants with CDH, as these factors are known to trigger pulmonary hypertension and affect the transition.[70-72] Additionally, adequate sedation decreases the time till intubation and this novel approach might therefore not increase the time till successful intubation.[70,71]

Medication prior to intubation

Our international survey on the use of medication prior to intubation in the delivery room in infants with CDH provided results that are not in line with current believes and evidence. First, although clinicians emphasised the need to improve pain and stress management, less than 20% of all infants currently receive sedation prior to intubation.[unpublished data] Additionally, in an even smaller group sedation was actually effective before intubation. Second, the combined use of a sedative and a muscle relaxant was scarce, whereas a combination of both enhances the effects of each medication.[unpublished data][73] The results emphasised the need for standardised protocols on medication in the delivery room, but they also underlined the challenge in determining the optimal regimen due to the high variation in medication regimens. Promising options mentioned in our survey include intranasal midazolam and intramuscular ketamine, but the time till effect of intranasal midazolam and the invasive nature of intramuscular administration question implementation. As mentioned before, we argue that it might be feasible to delay intubation until sedation is effective if non-invasive respiratory support is started and a nasogastric/orogastric tube is positioned. A faster alternative could be to administer medication via the umbilical vein in case of delayed cord clamping, but the degree in which this affects the benefits of PBCC is yet unknown. Another non-invasive and faster approach could be to use aerosolised sedation with for example ketamine or midazolam.[74] The diffusion of aerosolised sedation into the bloodstream may however be impaired by the reduced surface area of the lungs and the presence of fluid in the alveoli due to delayed lung aeration. As a final point, an innovative way to reach prompt sedation in

the infant and facilitate intubation is to administer medication to the mother before birth with an example being opioids such as pethidine.[75,76] Pethidine could however not be combined with non-invasive respiratory support as it suppresses spontaneous breathing in the infant, but short acting alternatives could be promising.[75,76] On the other hand, if spontaneous breathing after birth is deemed unlikely or insufficient, for example in those infants with expected severe pulmonary hypoplasia, the use of pethidine could be considered.

Physiological data

When aiming at individualised care for each infant with CDH during the transition, real-time and reliable measurements of important physiological parameters are required. Up till now, ovine models have provided valuable information on the fetal-to-neonatal transition in CDH because they allow for the monitoring of specific physiological parameters, such as pulmonary blood flow, that cannot be measured in clinical trials due to the need for invasive sensors. As such, current knowledge of the fetal-to-neonatal transition in CDH is largely based on ovine models.[2,50] In order to enhance our understanding of the transition and to evaluate disease severity at birth, it is preferable to assess all components of the disease triad, namely pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction. The infant's respiratory status is usually assessed with pulse-oximetry, yet current modalities often experience difficulties in obtaining an accurate signal within the first minutes, probably because of compromised perfusion, motion, or detachment due to the presence of vernix.[77] From a transition point of view, these first minutes are however the most interesting. Near-infrared spectroscopy (NIRS), providing measurements of cerebral tissue oxygen saturation, could overcome some of these limitations and might even provide an earlier signal than pulse-oximetry. Other parameters assessing the infant's respiratory status include flow and tidal volumes during mechanical ventilation, which could be implemented on a respiratory function monitor thereby guiding mechanical ventilation strategies.[56]

Early detection of the infant's heart rate is very useful because it provides information about all the components of the triad. Although international guidelines recommend the use of electrocardiogram (ECG) monitoring for a more accurate and rapid evaluation of heart rate compared to pulse-oximetry, not all centres use ECG during the transition.[78] Another interesting option includes the NeoBeat (NeoBeat Newborn Heart Rate Meter, Laerdal Medical) that provides heart rate measurements within seconds after birth and is easy-to-use.[79] As mentioned before, echocardiography is a modality that could improve our understanding of the neonatal transition and guide management after birth, including the use of early inotropes, but the feasibility of

implementation should be evaluated.[3,80-84] Real-time data collection during stabilisation has been implemented in the PinC trial and we expect that these data will add to the knowledge on the transition in CDH.[53]

The future: evidence-based care at birth

Multicentre RCTs in rare diseases are often challenging because of difficulties in reaching a sufficient number of participants within a reasonable time period, a lack of equipoise, or inconclusive results.[61,62,85-88] Hence, one can certainly challenge the idea of RCTs as a gold standard to generate evidence-based rationale for clinical practice.[86-92] We foresee a great benefit of changing the research environment from RCTs to the pragmatic alternative of prospective international registries capturing consecutive cases. To facilitate a transition towards registries, standardised outcome sets are required to guarantee high-quality data collection. For CDH specifically, a core outcome set for the first 28 days of life was recently published,[93] but we also encourage a core outcome set for the period thereafter.[94]

The future: individualised care at birth

Based on prenatal prediction methods, clinicians have identified whether the fetus is estimated to have severe lung disease. In case of estimated severe lung disease, the infant is intubated immediately after birth. Intubation is ideally initiated after adequate sedation has been reached, for example by means of antenatal administration of opioids to the mother. To anticipate on the time till successful intubation, the infant is intubated while the umbilical cord is still intact. After initiation of mechanical ventilation, intravenous access is obtained to enable administration of medications such as inotropes and pulmonary vasodilators. The indication for such medications is based on both echocardiography and respiratory parameters. Also, a nasogastric/orogastric tube with continuous suctioning is positioned. The umbilical cord is clamped after the infant's lungs have been aerated, which has been objectively determined.

In infants without estimated severe lung disease, non-invasive respiratory support is initiated immediately after birth and the umbilical cord is not yet clamped. A nasogastric/orogastric tube with continuous suctioning is positioned. Modalities such as echocardiography and the respiratory function monitor provide an early estimation of the cardiac and pulmonary disease severity. A consensus resuscitation algorithm, which takes both prenatal as well as perinatal data into account, guides further delivery room management including titration of respiratory support and initiation of medication such as pulmonary vasodilators or inotropes. If required, intubation is ideally only performed after reaching adequate sedation administered in a non-invasive way, but an alternative is the intravenous route. In all infants, the umbilical

cord is only clamped after the lungs have been aerated, which has been determined by means of ductus arteriosus shunting, lung ultrasound, or tidal volumes. Finally, the infant is transferred to the intensive care unit once sufficiently stabilised.

PART III | AFTER BIRTH

As mentioned before, the major components of disease severity in CDH are pulmonary hypoplasia, pulmonary hypertension, and cardiac dysfunction.[82] The severity of each component of this triad continues to vary greatly between infants after birth, leading to differences not only in the clinical presentation of postnatal problems, but also in the response to treatment. Hence, postnatal treatment regimens should consider this individual variety.

In infants with pulmonary hypertension secondary to CDH, the response to some of the routinely used vasodilators is suboptimal and this is believed to be caused by altered vasoreactivity due to changes in pathways involved in vasodilation and vasoconstriction.[95-104] Unfortunately, investigating the pulmonary vessels in alive infants is not possible. An interesting speculation is the presence of a placental-pulmonary connection during fetal development, underlined by the significant structural and functional similarities of both organs.[105,106] This speculation is supported by a study that showed a significant association between placental histopathologic lesions and the risk of neonatal bronchopulmonary dysplasia.[107] We tested our hypothesis that placental vessels could serve as a proxy for pulmonary vessels, providing an opportunity to understand the responses to pulmonary vasodilators. In our wire myography experiments, we confirmed that fetoplacental vessels obtained from CDH placentas showed significant alterations compared to those from healthy placentas.[unpublished data] These alterations are comparable to those observed in pulmonary arteries in CDH and may explain the limited response to inhaled nitric oxide and sildenafil.[95,96,108] In fact, pathways in which no alterations were found provide directions for postnatal treatment and in this, the use of medication targeting the prostaglandin E pathway, such as iloprost, seems promising.[109-112] Prostaglandin E results in pulmonary vasodilation thereby reducing pulmonary arterial pressure, but also in ductus arteriosus patency thereby decreasing the afterload of the right ventricle.[110,113,114] Several studies have already suggested that prostaglandin E1 could be administered in case of a restrictive ductus arteriosus and suprasystemic pulmonary hypertension, thus requiring prior echocardiographic evaluation.[110,113] One should also consider potential side effects such as apnoea, peripheral vasodilation, fever, and hypotension.[109] Aerosolised administration could reduce the systemic adverse effects while being equally effective

on non-CDH related pulmonary hypertension as inhaled nitric oxide.[115,116] Further evaluation of both infused and aerosolised prostaglandin E analogues in preclinical models could enhance our understanding of both the pulmonary and systemic effects.

Our data did not provide conclusive evidence on the similarities between placental and pulmonary vessels. To confirm the proposed placental-pulmonary connection, the similarities between endothelial cells of fetoplacental arteries and pulmonary arteries should be evaluated. The endothelial cells from placentas can be obtained easily after birth, but retrieval of endothelial cells from pulmonary arteries requires a more invasive procedure such as pulmonary artery catheterisation. Hence, this could only be done in infants undergoing such a procedure. Other than that, evaluation of the association between the fetoplacental alterations and postnatal pulmonary morbidity would increase our understanding of the clinical relevance of the placental-pulmonary connection. The existence of such an association would not only be interesting for infants with CDH, but also for infants with lung diseases due to other conditions.

Individualised postnatal treatment asks for early identification of those infants at a high risk of clinical deterioration. Targeted therapy in those cases could then avoid further worsening. For example, the need for ECMO therapy might be avoided if severe pulmonary hypertension would be identified and treated earlier.[117] We hypothesised that a continuous marker reflecting the infant's respiratory status identifies those infants with a high risk earlier and more reliably than currently used models.[118-126] In two retrospective studies, we demonstrated that the oxygen saturation index (OSI) is a marker that identifies infants with a high risk of clinical deterioration already in the first hours after birth.[117,127] Because of the OSI's excellent discriminative value for ECMO therapy, we encourage its use in decision rules for either referral to an ECMO centre or initiation of ECMO therapy in infants with CDH-related pulmonary hypertension.[117] Since SpO_2 is considered inferior to pO_2 in reflecting oxygenation, we emphasise that continuous OSI evaluation should be used as an additional early warning of clinical deterioration, and it should thus not replace oxygenation index measurements.[128-131] We foresee that the OSI is also useful in decision rules for otherwise critically ill infants, but validation in multicentre cohorts and other populations is required.

Other than that, the OSI's excellent predictive value for ECMO therapy and mortality could be further improved when combined with other markers reflecting cardiac or respiratory function.[117,132] Cardiac function is for example reflected by pro-b-type natriuretic peptide and left ventricular function, which would require blood sampling or echocardiography within the first hour after birth or already during the fetal-

to-neonatal transition.[80,81,133-141] Respiratory function could be reflected by carbon dioxide levels measured in blood samples or with transcutaneous monitoring.[119,142,143] A prediction rule that combines factors for cardiac and respiratory function provides a step towards implementation of big data. Many intensive care units already create big data by automated collection of continuous data during admission. Knowledge from these data could aid in developing prediction models and trend analysis models that enable personalised treatment in critically ill infants.[144] Interpreting big data can be prone to misinterpretation, so collaboration between clinicians and data professionals is essential to ensure accurate analysis and interpretation.[144]

The future: continuous individualised management

Instead of using one-size-fits-all guidelines for managing infants with CDH, an individualised approach is used already before birth and continuing throughout perinatal stabilisation and admission on the intensive care unit. This approach involves algorithms that are based on individual infant data including placental characteristics, epigenetic regulators, physiological data, respiratory support settings, echocardiographic measurements, and early biomarkers. Real-time dashboards display and interpret this information, allowing clinicians to monitor changes in the infant's condition over time. By using all available data, the dashboard can determine the risk for each infant and provide an early warning system to identify infants at risk of clinical deterioration. Therapy can then be adjusted early, potentially preventing severe complications and reducing morbidity and mortality.

In conclusion, despite the limitations inherent to a rare disease, any intervention should have a scientific base. We foresee that the use of big data will facilitate identification of new directions for evidence-based and individualised management, contributing to improved short-term and long-term outcomes of infants with CDH.

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PART V

| Appendices |

ABOUT THE AUTHOR

On 21st July 1994, Emily Jeanine Josina Oudshoorn was born in Wilnis, and her parents named her Denise. Four years later, her younger sister Demi was born. Denise completed her primary education in Wilnis and graduated with honours from Kalsbeek College in Woerden in 2012. Later that year, she moved to Leiden to study Medicine at Leiden University Medical Centre. After finishing her clinical rotations, Denise did her final internships in the Emergency Department at Haaglanden Medisch Centrum and at the Department of Paediatrics at Leiden University Medical Centre. In 2019, she obtained her medical degree. After her final internship, Denise was pleased to have the opportunity to start working under the supervision of Dr. Philip DeKoninck, with whom she began a PhD project focussed on optimising perinatal care for infants born with congenital diaphragmatic hernia. Alongside her PhD project, Denise completed multiple courses at the Netherlands Institute for Health Sciences and actively participated in several organising committees. In May 2023, Denise began working as a resident at the Department of Paediatrics at Reinier de Graaf Gasthuis in Delft. In her free time, Denise enjoys bouldering, playing football, riding a motorcycle, drinking coffee and spending time with her family and friends. Denise met her husband, Daniel, during her first year of medical studies, and they got married in 2016 in the presence of their loved ones. Since then, they have been living in Leiden.

LIST OF PUBLICATIONS

Horn-Oudshoorn EJJ, Blekherov AM, van den Bosch GE, Simons SHP, Knol R, te Pas AB, Reiss IKM, DeKoninck PLJ.
Sedation prior to intubation at birth in infants with congenital diaphragmatic hernia: an international survey on current practices.
Neonatology. 2023; 120(4):434-440.

Horn-Oudshoorn EJJ, Russo FM, Deprest JA, Kipfmueller F, Geipel A, Schaible T, Rafat N, Cordier AG, Benachi A, Abbasi N, Chiu PPL, de Boode WP, Sikkel E, Peters NCJ, Hansen BE, Reiss IKM, DeKoninck PLJ.
Survival in very preterm infants with congenital diaphragmatic hernia and association with prenatal imaging markers: a retrospective cohort study.
BJOG. 2023; 130(11):1403-1411.

Horn-Oudshoorn EJJ, Reiss IKM, DeKoninck PLJ.
Reply to "Oxygen saturation index: a trigger for neonatal transfer?".
Neonatology. 2023; 120(3):460.

Horn-Oudshoorn EJJ, Peters NCJ, Franx A, Eggink AJ, Cochius-den Otter SCM, Reiss IKM, DeKoninck PLJ.
Termination of pregnancy after a prenatal diagnosis of congenital diaphragmatic hernia: factors influencing the parental decision process.
Prenat Diagn. 2023; 43(1):95-101.

Horn-Oudshoorn EJJ, Vermeulen MJ, Knol R, te Pas AB, Cochius-den Otter SCM, Schnater JM, Reiss IKM, DeKoninck PLJ.
The oxygen saturation index as early predictor of outcomes in congenital diaphragmatic hernia.
Neonatology. 2023; 120(1):63-70.

Horn-Oudshoorn EJJ, Knol R, Cochius-den Otter SCM, te Pas AB, Hooper SB, Roberts CT, Rafat N, Schaible T, de Boode WP, van der Lee R, Debeer A, Kipfmueller F, Roehr CC, Reis IKM, DeKoninck PLJ.
Spontaneous breathing approach in mild congenital diaphragmatic hernia: a resuscitation algorithm.
Front. Pediatr. 2022; 10:945090.

Horn-Oudshoorn EJJ, Knol R, Vermeulen MJ, te Pas AB, Hooper SB, Cochius-den Otter SCM, Wijnen RMH, Crossley KJ, Rafat N, Schaible T, de Boode WP, Debeer A, Urlesberger B, Roberts CT, Kipfmueller F, Reiss IKM, DeKoninck PLJ.
Physiological-based cord clamping versus immediate cord clamping for infants born with a congenital diaphragmatic hernia (PinC): study protocol for a multicentre, randomised controlled trial.
BMJ Open. 2022; 12(3):e054808.

Horn-Oudshoorn EJJ, Vermeulen MJ, Crossley KJ, Cochius-den Otter SCM, Schnater JM, Reiss IKM, DeKoninck PLJ.
Oxygen saturation index in neonates with a congenital diaphragmatic hernia: a retrospective cohort study.
Neonatology. 2022; 119(1):111-118.

DeKoninck PLJ, **Horn-Oudshoorn EJJ**, Knol R, Crossley KJ, Reiss IKM.
Knowledge gaps in the fetal to neonatal transition of infants with a congenital diaphragmatic hernia.
Front. Pediatr. 2021; 9:784810.

Celen S*, **Horn-Oudshoorn EJJ***, Knol R, van der Wilk EC, Reiss IKM, DeKoninck PLJ.
Implementation of delayed cord clamping for 3 min during term cesarean sections does not influence maternal blood loss. *Both authors contributed equally.
Front. Pediatr. 2021; 9:662538.

Cochius-den Otter SCM, **Horn-Oudshoorn EJJ**, Allegaert K, DeKoninck PLJ, Peters NCJ, Cohen-Overbeek TE, Reiss IKM, Tibboel D.
Routine intubation in newborns with congenital diaphragmatic hernia.
Pediatrics. 2020; 146(4):e20201258.

Horn-Oudshoorn EJJ, Knol R, Te Pas AB, Hooper SB, Cochius-den Otter SCM, Wijnen RMH, Schaible T, Reiss IKM, DeKoninck PLJ.
Perinatal stabilisation of infants born with congenital diaphragmatic hernia: a review of current concepts.
Arch Dis Child Fetal Neonatal Ed. 2020; 105(4):449-454.

Horn-Oudshoorn EJJ, DeKoninck PLJ, Reiss IKM.
Neonatology is more than caring for micro-preemies!
Innovations and Frontiers in Neonatology. Pediatr Adolesc Med. 2020; 22:59–71.

PHD PORTFOLIO

	Year	ECTS
Courses		
Basic Course on 'R'	2019	1.8
Basic course Rules and Organisation for Clinical researchers (BROK)	2019	1.5
Basisdidactiek voor docenten (TtTI)	2019	0.5
CPO-course: Patient Oriented Research	2019	0.3
Follow-up Photoshop and Illustrator CC	2019	0.3
Scientific Integrity Course	2019	0.3
Biostatistical Methods I: Basic Principles	2020	5.7
Biomedical English Writing and Communication	2021	2.0
Intermediate course in R (BST02)	2021	1.4
Missing Values in Clinical Research (EP16)	2021	1.7
Repeated Measurements (CE08)	2021	1.7
National and international conferences		
3rd Congress of Joint European Neonatal Societies - Poster presentation	2019	1.0
TULIPS Jonge Onderzoekers Dag	2019	0.3
4th Congress of Joint European Neonatal Societies - Poster presentation	2021	1.0
17th European Congress of Perinatal Medicine - Two oral presentations, *winner best oral presentation Neonatology*	2021	1.0
9th Congress of the European Academy of Paediatric Societies - Poster presentation	2022	1.0
18th European Congress of Perinatal Medicine - Oral presentation	2022	1.0
26th International Conference on Prenatal Diagnosis and Therapy - Poster presentation	2022	1.0
International Congenital Diaphragmatic Hernia Symposium - Three oral/ poster presentations	2022	2.0
32nd World Congress on Ultrasound in Obstetrics and Gynecology - Two oral/poster presentations	2022	1.0
Teaching activities		
Coaching medical students (n=12)	2019-2022	2.0
Supervising medical students (Research project in minor)	2020	0.5
Supervising medical student (CAT)	2020	0.5
Additional activities		
Sophia Researchers Network (SOV) Board	2020-2022	2.0
Sophia Research Day 2020	2020	1.0
Sophia Research Days 2021	2021	1.5
Research meetings Neonatology	2019-2023	2.0

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Denise