Pulse oximetry screening for critical congenital heart disease and relevant newborn pathology in the Netherlands

Pulse Oximetry Leiden Amsterdam Regional Screening Study

POLAR study

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**Background/Rationale**

Congenital Heart Disease (CHD) is the most common group of congenital malformations and is a leading cause of infant death in the developed world.\(^1\) It is estimated that in the Netherlands 1280 children with CHD are born every year, including 250 newborns with critical CHD (CCHD), who require an interventional procedure or cardiac surgery in the first month of life.\(^2\) In the last decennia progress in pediatric diagnostics and cardiac surgery has led to a considerable improvement in survival of infants with CCHD.\(^3\) Early detection of CCHD in both pre- and postnatal period is vital for the prognosis.\(^4\) However, despite the introduction of antenatal echocardiography screening at 20 weeks of gestation in the Netherlands in 2007, recent data from the Amsterdam-Leiden region show that still around 50-60% of CCHD cases are antenatally missed.\(^5\) Also, after birth CCHD is often missed as physical examination alone is not sensitive enough for screening.\(^4,6\)

Newborns with CCHD may develop severe cyanosis and/or heart failure in the first days of life, often resulting in a poor physical condition or even death, before corrective surgery can be performed. This influences not only the survival rate of this group of patients, but also, in case of survival, has long term consequences due to severe complications such as brain injury.\(^3,4,7-11\)

In the Netherlands 125 newborns with CCHD per 180.000 births are missed every year (0.7 per 1000 births).\(^2\) Approximately 40% (50/125) of these infants are presented in the hospital in a very poor clinical condition and studies have shown that the mortality rate of this critically ill CCHD group is 5.5 times higher as compared to the total CCHD group (mortality in the first month of life 50% versus 9%).\(^3,4,12\) Early detection of CCHD in the Netherlands has not only the potential to prevent death in 25 infants, but also to decrease long-term morbidity. There is little data available, but it is expected that early detection can decrease the incidence and severity of brain injury.\(^12\) Data have shown that the incidence of brain injury is 55% in the critically ill CCHD group and lower (10%) in the total CCHD group.\(^11,12\)
Pulse Oximetry (PO) is a simple and non-invasive method for screening cyanotic CHD in low risk infants.\textsuperscript{13,14} Previous studies have shown a sensitivity of 76.5%, a specificity of 99.9% and a false positive rate of 0.14%.\textsuperscript{15} False-positive tests included persistent pulmonary hypertension of the newborn in 37.5%, sepsis in 32.5% and no pathology was found in 30%.\textsuperscript{16} American and English studies showed that PO screening for CCHD reaches a 90% chance of being cost-effective.\textsuperscript{17,18} PO 24-48 hours after birth is now recommended by the Human Health Services and has recently been implemented in Switzerland, Sweden, Abu Dhabi, many states of the US and 25% of maternity wards in the United Kingdom. In these countries the screening normally takes place in a hospital setting prior to discharge.\textsuperscript{12,19}

In the Netherlands the perinatal health care of low risk infants is unique as compared to other countries. In 33% of all cases perinatal care and deliveries of low risk infants are supervised by community based midwives, either at home birth (17.4% of all births), at a birth clinic or in a hospital. When a mother gives birth in the hospital and there are no risk factors or complications, she is discharged from the hospital within 5 hours after birth. The baby will be checked upon at home by the midwife one or two days later. In case of home birth, the midwife stays until approximately three hours after birth to return for follow-up at day two or three, with the day of birth counting as day one.

To determine the feasibility of PO screening for CCHD in the Netherlands, the Leiden University Medical Center conducted a feasibility study in the Leiden region since October 2013. During the study period of one year community based midwives from all 14 regional practices, the Rijnland Hospital in Leiderdorp, the Diaconessenhuis in Leiden and the Leiden University Medical Center performed PO screenings for CCHD in term infants.

This study showed that 99% of term infants of which parents approved consent, can be screened when using the adapted protocol as is shown in figure 1. These percentages indicate that PO screening for CCHD is feasible in the Netherlands.\textsuperscript{20} In 17/33 (52%) of all false positive screenings, other important pathology was found, including 5 non-critical CHD,
5 cases of PPHN or wet lung, 3 infants with infections treated like sepsis, 1 meconium aspiration syndrome, 2 infants with polycythemia above treatment level.

Although studies have shown the benefits of implementing PO for CCHD screening, implementation in the Netherlands remains a controversial issue. The question remains if it is possible to reach the same benefits if the PO screening would be implemented in the Netherlands as compared to other countries. To perform an adequate PO screening in the Netherlands implicates that all 1854 midwives with home practices would need to use a pulse oximeter as standard of care. It remains to be determined whether the benefit of CCHD screening weighs against the costs of providing all midwives with a pulse oximeter. The accuracy of PO for CCHD screening in the Netherlands using the adapted protocol is currently unknown and to assess this a large implementation/accuracy study would be needed.

In addition, symptoms of transitional problems (such as wet lung, persistent pulmonary hypertension), polycythemia and sepsis can be difficult to recognize and a delay can occur in referral when the infants’ condition has worsened. Previous studies and our feasibility study showed that pulse oximetry screening is also a useful tool for early detection of these potential life-threatening conditions.\textsuperscript{21-24} The detection of these conditions will be taken as secondary outcome since, together with detecting CCHD, the PO screening has the potential to decrease perinatal morbidity and mortality.

Also, a higher percentage of false positive referrals could be anticipated in the Netherlands, possibly causing distress in parents and midwives supervising the births. However, it has been shown in previous screening studies that in 37-70% of false positive referrals other morbidities were diagnosed that needed early treatment.\textsuperscript{25} For this reason implementation of the screening in the Netherlands also has the potential to increase safety of home birth deliveries.
Aim

To determine the accuracy and cost-effectiveness of CCHD screening in the Netherlands in hospitals and at home by community based midwives.

Methods

Design

A prospective non-randomized multi-centre study

Setting

All community based midwifery practices and hospitals in the Amsterdam-Leiden-region. This region consists of three academic hospitals (Leiden University Medical Center, VU University Medical Center Amsterdam and Academic Medical Center Amsterdam) and 12 regional hospitals.

The screening is already standard care in the Leiden region and will be enrolled in the Haarlem and Amsterdam region.

The Leiden University Medical Center will be the coordinating and organizing center of the Pulse Oximetry Screening the Netherlands Study.

Study population

All infants born in the Amsterdam-Leiden region (30,000 births/year) will be included (birth at home or in hospital). Only the infants where pre and post ductal PO is used for monitoring
at least 24 hours for other reasons, and infants who already underwent echocardiography will be excluded.

**Devices**

All 350 community based midwives with home practices in the Amsterdam-Haarlem-Leiden region will be provided with a portable pulse oximeter that secures reliable oxygen saturation values in newborn infants, overcoming limitations related to low perfusion and motion artefacts. A portable pulse oximeter will also be used at the delivery rooms and at the maternity wards of the participating hospitals.

Before start of the study all midwives will receive training in using the PO and all caregivers in and outside the hospital will be instructed concerning the logistics.

**Measurements**

The oxygen saturation will be measured at least 1 hour after birth and, if negative, at day 2 or 3 of the infant's life (day 1 is day of birth). Oxygen saturation will be measured with the probe placed at the right hand (pre-ductal) and consecutively at either foot (post-ductal). The probe will be attached for at least 2 minutes per measure, until a stable value is obtained.

In case of a home birth all measurements will be performed by the community midwife. The second measurement will be performed at the follow-up visit at day of life two or three.

In case of a delivery in hospital the first measurement (at least 1 hour after birth) is performed in the delivery room by the clinical midwife, the obstetric nurse or the gynaecologist (or registrar). If mother and infant are discharged within 24 hours, the second measurement is performed at home by the community midwife. In case of hospitalization until at least 24 hours after birth, the second measurement is performed at the obstetric department by the obstetric nurse. The transfer letter for the community midwife should contain information on the performance and timing of the second measurement and the
screening should be mentioned in the telephonic hand over from the obstetric department to the community midwife.

Figure 1 shows the decision tree as described below.

Positive screening

The screening is considered positive if:

- Pre or post ductal SpO₂ <90%
- Two repeated measurements with:
  - Pre and post ductal SpO₂ <95%, or
  - Difference between pre and post ductal SpO₂ >3%

All infants with a positive screening will be medically evaluated. Depending on the place where the positive screening is obtained there are different pathways for the referral of infants with a positive screening.

Positive screening at home

In case of a positive screening at home the infant will be referred to a participating hospital. During working hours the infants will be seen at the emergency outpatient clinic.

Positive screening in a hospital

If a positive screening is obtained at the delivery room or obstetric department in a regional hospital, the pediatric registrar or paediatrician will examine the infant. The SpO₂ will be checked once more and a thorough physical examination will be performed. If there is a clear non-cardiac cause for the abnormal SpO₂ values, this pathology will be treated. If no non-cardiac cause can be detected, or if SpO₂ values do not normalize, the local pediatric
cardiologist or the consultant pediatric cardiologist of an academic center will be consulted to discuss the timing and planning of an echocardiogram.

**Negative screening**

In case of a negative screening, there is no follow-up. Local registries and mortality databases will followed-up for possible CCHD until at least one month after the study has ended.

All births are registered in the Perinatal Data Registry.

**Pilot period**

Before starting with the implementation study, a pilot period of 3 months will be used to train and instruct the midwives and hospitals and to assure optimal screening methods.

**Primary outcome**

In this study the primary end point will be the accuracy of PO screening for CCHD. The accuracy is embodied in the sensitivity, specificity, false positive rate, false negative rate, positive and negative predictive value.

**Secondary endpoints**

Cost-effectiveness

Problems identified in the use of PO in home setting

Problems identified with referral logistics

Other pathology detected with screening with PO
Database

All important parameters from pregnancy and birth of all included infants will be collected using an electronic Case Report Form (CRF). The data from the CRF will be automatically collected in an electronic database. All data in the database will be de-identified by using the CRF number. It will contain antenatal data, basic parental and patient characteristics. Results of antenatal echocardiography screening and result of the PO screening will be noted. In case of referral, the final diagnosis will be noted. As the academic hospitals are the only referral centres for congenital heart disease in the Amsterdam-Leiden-region, we are able to identify the infants where CCHD is missed because 1) they were not included or 2) the screening test was false negative. Diagnosis and outcome of the referred infants diagnosed with CCDH will be noted.

All data will be entered into SPSS database (SPSS for windows, version 20.0, 2011, Chicago, IL).

Parental information

Neonatal screening for CCHD is implemented as universal screening in the United Kingdom, United States of America, the Nordic-European countries, Abu Dhabi and is also performed in parts of other European countries, such as Germany, France and Spain. Pulse oximetry measurements are non-invasive, there is no potential risk and international studies have shown that pulse oximetry screening detects potential life-threatening pathology in newborns.

We have chosen for a passive consent (opt out: after the parents are fully informed they can decide to refuse the screening) for the following reasons:

- The measurement is fast, non-invasive and not cumbersome to the baby. The pulse oximetry screening is currently implemented in the routine neonatal examination postnatally
in the Leiden region at this moment. This change in policy was the result of the feasibility study, where we not only showed the screening was feasible to do, but also detected important pathology. Therefore, there is no need for written consent in the Leiden region;

- Studies have shown that an opt-in approach results in lower response rates and a biased sample, with inclusion of persons with a higher education and social economic status. In the feasibility study in the Leiden region, refusal of participation hardly occurred (only in 15 infants in a one year period, with over 2600 infants included). However, inclusion rate of eligible infants was on average 70% in our According to a questionnaire filled in by performers of the screening, reasons for not including patients were high work load on the delivery rooms, forgotten to ask for consent and acute maternal pathology. Our opinion is that all parents and infants should have the same chance of being included in this study. In our feasibility study parents of an infant with an antenatal undetected aorta interruption were not approached for consent and the CCHD was not detected early, but referred on day 3 with signs of circulatory shock;

- By using an opt-out strategy we can reach more parents and a more representative group and we will be able to include enough infants to achieve the sample size.

-There is no harm, risk or cost for parents and infants when PO screening is performed. Then only risk that could occur is a false positive referral where there is no pathology. In the feasibility study this risk was <0.5%;

-There are no burdens for implementation of the screening in the Netherlands, except from the unknown sensitivity, specificity and false positive rate in the unique Dutch perinatal care system with a high percentage of births supervised by a community midwife and early discharge after a delivery in hospital;

-Neonatal PO screening is currently implemented as standard of care in the United States and increasingly implemented in the European countries. It is expected that this will also be
become standard care in the Netherlands. In the pilot study in the Leiden region we have shown that the PO screening is feasible in the Dutch perinatal setting and other potential life-threatening morbidities can be detected early. However, to assess the sensitivity, specificity and cost-effectiveness, a larger sample size is needed;

Parents will be informed verbally during the antenatal midwifery visits and by posters in the waiting room. Also, full information on the screening will be publicly available on a website and parents are informed verbally once more before the first physical examination (which includes the PO screening) of the infant is performed.

**Sample size**

Using the one-sample sensitivity and specificity sample size calculation for diagnostic tests, a total sample size of 20,000 newborn infants (which includes 40 newborns with CCHD assuming a prevalence of 0.2%) achieves 82% power to detect a change in sensitivity from 52% to 75% using a two-sided binomial test; and 95% power to detect a change in specificity from 99.3% to 99.5% using a two-sided binomial test.\(^{30}\) The target significance level is 0.05.

In the Amsterdam-Leiden district, yearly approximately 30,000 infants are born, which accounts for 17% of the total birth rate in the Netherlands.\(^{31}\)

Previous studies using PO for CHD screening reported various percentages of infants that were able to be screened (86-100%).\(^{15}\) Interim results of CCHD screening in our region, show that 99% of all infants with parental consent were screened, leading to 2432 screened infants in a period of 10 months. Parents of 21 infants refused the screening in that period.

We aim to screen at least 90% of the infants born in the Amsterdam-Leiden region. As the logistics and care paths in this region are similar to other parts of the country, we expect that the percentage of infants we are able to screen reflects the coverage ratio when this screening will be performed in the Netherlands.
As participation is completely voluntary, we can only screen the infants of parents that didn’t opt-out for the screening. However, we have performed a similar study testing the feasibility of using PO screening and the inclusion rate (99%) reflected the enthusiasm of parents for the use of PO. In addition, we do not expect that parents would refuse a free non-invasive test for a potential life-threatening disease.

**Statistical analysis**

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<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Negative screening</td>
<td>C</td>
<td>D</td>
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Sensitivity = A/(A+C); specificity = D/(D+B); false positive rate = B/(A+B+C+D); false negative rate = C/(A+B+C+D); positive predictive value = A/(A+B); negative predictive value = D/(C+D)

Sensitivity, specificity, false positive rate, false negative rate, positive predictive value and negative predictive value will be calculated for the protocol with two measurement time points and for a strategy with only the first measurement point.

**Cost-effectiveness**

A cost-effectiveness analysis will be performed from the societal perspective. A decision-analytic model will be used to compare the relative cost-effectiveness of a strategy in which pulse oximetry screening is added to routine practice with the strategy of routine practice alone\textsuperscript{17,18}. As prevention of preoperative collapse is likely to be associated with lower postoperative mortality and morbidity, the primary outcome measure is ‘timely diagnosis’,
that is diagnosis made preoperatively before collapse or death occurs.\textsuperscript{17,18} In an explorative analysis the time horizon will be extended by assessing lifelong effectiveness and costs. In this analysis quality-adjusted life-years (QALYs) will be used as outcome measure.

The decision-analytic model developed by Knowles et al. will be used as starting point, but will be adapted to the Dutch situation.\textsuperscript{18} Data from the implementation study will be used to adapt the model. Cost of pulse oximetry will be based on a detailed cost price analysis. Material costs, staff time, transportation costs and treatment costs will be evaluated. In the last months of the implementation study a time-and-motion study will be performed. In this study all staff across the study sites will be asked to record the time it took them to carry out the test and record the result during one week. This study will be done close to the end of the study, as initial difficulties with equipment, technique or protocol will probably be solved. Also the time taken for clinical evaluation after positive screenings and timing of echocardiography in case of persistent hypoxia will be measured. Other resource use will be valued using standard prices.\textsuperscript{32}

The total costs and effects will be assessed for both strategies and a cost-effectiveness acceptability curve (CEAC) will be produced comparing the probability that pulse oximetry screening is cost-effective for different values of the willingness to pay for two screening measurements and for only the first screening measurement.
Patient Safety

Pulse oximetry is a non-invasive test and measuring oxygen saturation is considered standard of care in high risk infants at birth. There are no patient safety issues, but it is possible that it will cause unnecessary distress in midwives and parents when a referral follows after a false-positive screening.

Relevance of this study

Compared to the neighbouring countries, the Netherlands lags behind with the implementation of this screening method. When considering the unique perinatal healthcare of low risk pregnancies, the question remains if implementing this test in the Netherlands would be as accurate and cost-effective as previously reported. However, at this moment every year 125 infants with CCHD are missed and late presentation will certainly decrease the chance for survival and increase long term morbidity. This implementation study will answer the question if PO screening for CCHD should be implemented. This study will be a step in improving the survival and prognosis of infants with CCHD in the Netherlands.

False positive screenings can also detect other pathology, such as infections or persistent pulmonary hypertension.\(^\text{25}\) As treatment for these pathologies is also important, pulse oximetry screening can improve the safety of newborns in the Netherlands, especially those who are born at home.
References


29. Woolf SH, Rothemich SF, Johnson RE, Marsland DW. Selection bias from requiring patients to give consent to examine data for health services research. *Arch Fam Med.* 2000;9:1111-1118.


Figure 1 Flowchart of PO CCHD screening
Positive screening

Referral to hospital

Clinical evaluation including pre- and post-ductal SpO2 measurement

Normal at clinical evaluation AND normalized SpO2 values

- False positive screening

Clear non-cardiac pathology

- False positive screening

Persistent abnormal SpO2 values without clear non-cardiac pathology

- Echocardiography

- CCHD

  - YES
    - True positive screening
  - NO
    - False positive screening

Figure 2 Flowchart Positive Screening