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[Pulsoximetri screening för upptäckt av hjärtmissbildningar hos nyfödda]

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Statement from the Regional HTA Centre 2011-05-25

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HTA-centre in Region Västra Götaland - Presentation

- Systems for grading evidence

Summary of the Health Technology Assessment

- **Method and patient group**

Screening with pulse oximetry (POX) of asymptomatic newborns before discharge from the well baby nursery in order to detect critical congenital heart defects (CCHD).

- **Question at issue**

What is the diagnostic accuracy for pulse oximetry in screening of asymptomatic newborns before discharge from the well baby nursery and does pulse oximetry screening, alone or in addition to physical examination, lead to increased detection of critical congenital heart disease and reduced mortality and morbidity?

PICO (Patient, Intervention, Comparison, Outcome)

P = Asymptomatic newborns

I₁ = POX, regardless of location of the pulse oximeter probe, combined with physical examination of the newborn at any age before discharge from the well baby nursery

I₂ = POX under the same conditions, but with no physical examination

C = Physical examination

O = Primary outcome:
Sensitivity and specificity in detecting CCHD using echocardiography as reference standard

Secondary outcomes:

1. Undetected CCHD at discharge
2. Mortality in newborns with CCHD
3. Morbidity in newborns with CCHD

- **Studied risks and benefits for patients of the new health technology**

POX and physical examination combined or POX alone has good diagnostic accuracy for CCHD with high specificity and low false positive rates.
(Moderate level of evidence)

POX and physical examination combined versus physical examination alone was associated with a reduced risk for being discharged with undetected CCHD.
(Low quality of evidence, GRADE ⊕⊕)

POX and physical examination combined versus physical examination alone was associated with no statistical difference in mortality in newborns with CCHD.
(Very low quality of evidence, GRADE ⊕)

POX and physical examination combined versus physical examination alone was associated with a decreased risk for morbidity (severe acidosis) in newborns with CCHD .

(Low quality of evidence, GRADE ⊕⊕)

- **Ethical questions**

Does a false-negative POX test result lead to a delay in diagnosis of CCHD?

Does a false-positive POX test result cause parental concern?

- **Economical aspects**

Previous studies have shown that adding POX to physical examination of asymptomatic newborns is likely to be a cost-neutral screening strategy for CCHD. We found a higher estimated cost per timely diagnosis due to a longer expected time needed for a POX screening examination.

Conclusion:

POX screening is a non-invasive method with a good diagnostic accuracy to detect CCHD in asymptomatic newborns before discharge from the well baby nursery. There are still insufficient data to evaluate whether this also will affect mortality and morbidity. The costs associated with an introduction of the method at Sahlgrenska University Hospital are estimated to be around 800.000 SEK during the first year, and thereafter the annual cost will be somewhat lower.

Which health technology or method will be assessed?

Pulse oximetry (POX) screening for congenital heart defects in newborns

1a. Who will lead the project?

Ulla-Britt Wennerholm, MD, PhD, Associate Professor, Division of Obstetrics, Sahlgrenska University Hospital, Göteborg, Sweden

Co-workers:

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Ola Hafström, MD, PhD, Division of Neonatology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Göteborg, Sweden

1b. Who posed the question?

Ingemar Tessin, Director, Division of Neonatology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Göteborg, Sweden

Anneli Falk, Director, Division of Obstetrics, Sahlgrenska University Hospital, Göteborg, Sweden

1c. Additional parties who posed the question?

Jimmy Kero, Chief Operational Officer, The Queen Silvia Children's Hospital and Women's Clinic, Sahlgrenska University Hospital, Göteborg, Sweden

1d. Other participants, from the HTA centre

Annika Strandell, MD, PhD, Associate Professor

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1e. Are there any conflicts of interest for the proposer or any of the participants in the work group?

No conflicts of interest

Disease/disorder of Interest and Present Treatment

2a. Disease/disorder of interest and its degree of severity

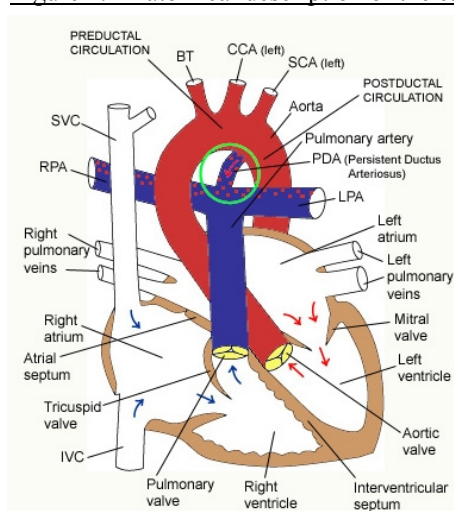
Congenital heart defects (CHD) are one of the most common birth defects. They account for about 6-10% of all infant deaths and 20-40 % of deaths caused by congenital malformations (Abu-Harb, 1994, Lloyd-Jones, 2009).

Critical congenital heart defects (CCHD), i.e. hearts with circulation dependent on an open ductus arteriosus or cyanotic lesions, pose a particular challenge due to the need for early diagnosis (Richmond 2002, Koppel, 2003, Wren, 2008, de-Wahl Granelli, 2009, Hoffman, 2011). Most of potentially life threatening CCHD are duct dependent with critical obstruction of blood flow to the pulmonary or systemic circulation. The former could be a pulmonary or a tricuspid atresia, and the latter a hypoplastic left heart syndrome, a severe aortic stenosis, a coarctation of the aorta or an interrupted aortic arch. A small proportion of CCHD are life threatening due to severe heart failure or cyanosis that develops early but unrelated to the closure of the arterial duct (Mellander, 2006).

An early discharge from the well baby nursery poses a higher risk for ductal closure outside hospital with severe consequences for the infant. Newborns with a coarctation of the aorta or an interrupted aortic arch are particularly at risk of a missed diagnosis. The closure of the duct may lead to hypoxia and acidosis with severe heart failure and even circulatory collapse. The prognostic outcome for these babies is poor and a late diagnosis usually leads to a higher operative mortality, a longer stay in the intensive care unit, and a higher incidence of other serious complications such as neurological dysfunction, and in some cases even death. Therefore a timely diagnosis of CCHD is of utmost importance.

In the Swedish study by de-Wahl Granelli the risk for an infant with a duct dependent CCHD to leave the hospital without being diagnosed was 28 % if the infants did not have a screening examination with pulse oximetry (POX) performed at the well baby nursery before discharge (de-Wahl Granelli, 2009).

Figure 1. Anatomical description of the cardiac circulation



The blood returns from the upper and lower part of the body through SVC (superior vena cava) and IVC (inferior vena cava) into the right atrium. It then flows through the tricuspid valve into the right ventricle, which pumps the blood through the pulmonary valve, into the pulmonary artery leading the blood to the right and left lung by dividing into the right (RPA) and left (LPA) pulmonary artery (branches).

The blood is oxygenated and returns to the left atrium via the right and left pulmonary veins and continues through the mitral valve into the left ventricle, which pumps the blood through the aortic valve into the aorta and further to the systemic circulation providing every part of the body with fully saturated blood (in normal conditions).

In most cases the aorta (aortic arch) is left-sided and branches into BT (brachiocephalic trunk) as the first neck vessel, CCA (left common carotid artery) as the second neck vessel and SCA (left subclavian artery) as the third neck vessel.

If a PDA (persistent ductus arteriosus) is present, it is usually positioned as shown in Figure 1, between the aorta and the pulmonary artery. When measuring oxygen saturation by pulse oximetry, it is important to use the right arm to be certain of measuring saturation preductally and either foot to be certain of measuring postductally according to the anatomy.

2b. Prevalence and incidence of the disease/disorder

The reported incidence of CHD varies in different studies. It is estimated to occur in about 8-12 infants per 1000 live births (excluding bicuspid aortic valves and small atrial or ventricular septal defects) (Hoffman, 2002).

In Sweden there are about 112 000 live births per year (Medicinska födelseregistret, 2009). This would mean a total of 900-1300 infants born with a CHD per year. In Region Västra Götaland, 19 135 children were born in 2009, of which approximately 150 – 230 then would have a CHD. About one to two babies per 1000 live births have a CCHD (Richmond 2002, Koppel, 2003, Wren, 2008, de-Wahl Granelli, 2009, Hoffman, 2011).

The reported birth prevalence of CCHD will most probably decrease with the increasing use of prenatal screening examinations by fetal echocardiography. Many times a prenatal diagnosis will lead to termination of the pregnancy of fetuses with severe/complex CHD. For instance it is estimated that 50% of pregnancies with a fetus with hypoplastic left heart syndrome is terminated today in Region Västra Götaland.

2c. Present treatment of the disease/disorder in the out-patient setting/ in-patient setting

Antenatal screening for congenital heart disease

Presently, an antenatal ultrasound during the 18th-19th week of gestation is offered to all pregnant women in Region Västra Götaland. The purpose of the ultrasound is to date the pregnancy, to detect multiple fetuses, and to detect serious fetal malformations. The four-chamber ultrasound view of the fetal heart is the most widely used method to examine the fetal heart. However, anomalies of the right and left ventricular outflow, i.e. transposition of the great vessels and coarctation of the aorta are often undetected at this examination. Midwives in the Region Västra Götaland are currently trained to image the outflow tract of the fetal heart, in order to improve detection rate of these great artery abnormalities. When a congenital cardiac malformation is suspected the pregnant woman is referred for a complete fetal echocardiography at The Queen Silvia Children's Hospital. An extended screening programme for fetal cardiac malformations is under development, and its use varies widely in different parts of Sweden.

In London pediatric centers 50-55% of babies with significant CHD are diagnosed prenatally as compared to 20-30% in the centers outside London (Sharland, 2010).

Physical newborn examination

A pediatric resident, a pediatrician or a neonatologist examines all newborn babies. Usually this is done during the first 24 hours of life. The purpose of this examination is to detect any abnormal adaptation to extra-uterine life, and to detect congenital malformations. Assessment of the cardiovascular system includes evaluation of vitality, peripheral circulation, respiration, heart rate, rhythm, murmurs, femoral and axillary pulse volume, and presence of cyanosis. A recent Swedish study of maternity care reported that the age at the time of the first examination varied from 6 to 72 h (Ellberg, 2008). In 23 of 48 hospitals a second physical examination was also performed. Sometimes this second physical examination took place during an outpatient visit three days or later after birth.

Physical examination in the child welfare clinic (barnvårdscentral, BVC)

During infancy and childhood regular clinical examinations are scheduled and performed by pediatricians or general practitioners in the child welfare clinic (BVC). The first one occurs at six to eight weeks of age. These physical examinations rarely result in the detection of CCHD.

2d. Number of patients per year who undergo current treatment regimen?

Presently, all newborns are screened for CHD by physical examination in the well baby nursery. During 2010 this resulted in 290 (290/11 215 = 2.6%) referrals from the Obstetric department at Sahlgrenska University Hospital to the Pediatric Cardiology unit at Queen Silvia Children's Hospital for further diagnostic evaluation including echocardiography.

2e. The normal pathway of a patient through the health care system

If an otherwise healthy newborn is detected to have heart murmur on the physical examination, a pulse oximetry (POX) is performed. If the oxygen saturation is normal a second clinical examination is scheduled the following day. Often the adaptation of blood circulation is not complete during the first day of life and a cardiac murmur can be a sign of this. If the murmur persists on the following day, the infant is referred for echocardiography.

Newborns with a diagnosed CCHD are referred to the Pediatric Cardiology unit where they are closely monitored and kept cardiopulmonary stable. A decision is thereafter taken how to proceed with either palliation and/or corrective surgery.

2f. Actual wait time in days for medical assessment /treatment

Newborns with a suspected CCHD are usually examined on the same day at the Pediatric Cardiology unit at Queen Silvia Children's Hospital.

For well being newborns with a cardiac murmur, who have been discharged home, the actual wait time is usually no more than two (to four) days after referral.

Present Health Technology

3a. Name/description of the health technology at issue

Pulse oximetry (POX) is a non-invasive method for measuring oxygen saturation. There are different kinds of pulse oximeters measuring either *functional* or *fractional* oxygen saturation. *Functional* saturation refers to the ratio of oxygenated haemoglobin (oxyhaemoglobin) to all haemoglobin capable of carrying oxygen. *Fractional* saturation refers to the ratio of oxygenated haemoglobin to all haemoglobin measured (including that which does not carry haemoglobin = deoxyhaemoglobin or dyshaemoglobins, i.e. MetHb or COHb). Different investigators have used different cut-off values for the lower limit of normal saturation, between 92 and 96%, with most of them using 95% (Table 1, Appendix 1). Fractional saturation is approximately 2% lower than functional.



The probe location is postductal (either foot) or both pre- and postductal (right hand and either foot). The use of pre- and postductal probe location (with a difference of >3% as abnormal) can improve detection of rare cases of transposition with a large patent ductus arteriosus. In such cases the leg saturation may exceed 95%. Also, in rare cases of a coarctation or an interrupted aortic arch the right arm saturation may be 99% and the leg saturation 95%. The sensitivity of POX screening was not influenced by probe location in the studies included in this analysis. The POX probe is attached until a stable recording is observed which usually takes no more than two minutes.

Timing of the test influences the specificity of POX screening. Studies of normal oxygen saturation soon after birth showed that saturation was fairly stable over the first 48 h with a slight tendency to rise 12-24 h after birth (Hoke, 2002). Early POX screening, i.e. at four hours of age was associated with lower specificity since newborns with delayed pulmonary adaptation presented with low POX values (Sendelbach, 2008).

Newborns with other lung problems or infections may also have low POX-values leading to earlier diagnosis of these conditions.

3b. The work group's understanding of the potential value of the health technology

In Sweden, the average length of stay in the well baby nursery after vaginal delivery has decreased from an average of six days in 1973 to two days presently (Medicinska födelseregistret, 2009). In parallel with the reduced length of stay, the proportion of infants leaving hospital with undetected CCHD has increased (Mellander, 2006). Currently 28 % of all newborns with CCHD and duct dependent circulation are discharged undiagnosed from well baby nurseries in Sweden, which do not use POX screening (de Wahl Granelli, 2009). These infants are at increased risk of circulatory collapse and severe complications.

The rationale for screening of newborns with POX is to identify newborns with CCHD already in the hospital before circulatory collapse. This would allow timely initiation of intensive care before surgical correction, and at the end a much better outcome and a shorter hospital stay.

One HTA report from UK (Knowles, 2005) and one systematic review (Thangaratinam, 2007) has previously evaluated the accuracy of POX screening to detect CHD in asymptomatic newborns. The conclusion was that POX was a promising screening strategy with a high specificity and with very low false positive rates. However, they also concluded that further research concerning timing, value of repeat examination and psychosocial effects was needed.

In the Swedish study by de-Wahl Granelli the addition of POX screening to newborn physical examination reduced the risk to leave the hospital with an undetected CCHD and duct dependent circulation from 28% to 8%. This would correspond to reduction of the number of such infants discharged from hospital from seven to two per year in Region Västra Götaland (and in Gothenburg four to one). In Sweden, the corresponding estimated reduction would be from 40 to 11 infants per year (112 000 infants were born in Sweden in 2009).

By adding POX screening to physical newborn examination, sensitivity for detecting CCHD would increase from 62,5% to 60,0-88,6% (Tables 2a and 2c) according to the studies included in this analysis. The sensitivity for POX screening alone for detecting CCHD is 62%-97% (Table 2b). These estimations are based on unblinded observational cohort studies with low, moderate and high quality of evidence.

The accuracy of POX screening for detecting CCHD is different for duct dependent pulmonary and duct dependent systemic circulation. Nearly all cases with duct dependent pulmonary circulation or cyanotic CCHD are detected with POX screening. Many cases with duct dependent systemic circulation remain undetected after screening with POX and newborn clinical examination as well as after screening with antenatal ultrasound.

POX screening should not replace newborn clinical examination but may be used as a complementary examination in order to increase the detection rate of CCHD before discharge from hospital.

3c. The central question for the current HTA project

What is the diagnostic accuracy for pulse oximetry in screening of asymptomatic newborns before discharge from the well baby nursery and does pulse oximetry screening, alone or in addition to physical examination, lead to increased detection of critical congenital heart disease (CCHD) and reduced mortality and morbidity?

3d. PICO (P= Patients, I= Intervention, C= Comparison, O=Outcome)

PICO:

P = Asymptomatic newborns

I₁ = POX, regardless of location of the pulse oximeter probe, combined with physical examination of the newborn at any age before discharge from the well baby nursery

I₂ = POX under the same conditions, but with no physical examination

C = Physical examination

O = Primary outcome: Sensitivity and specificity in detecting CCHD using echocardiography as reference standard

Secondary outcomes:

1. Undetected CCHD at discharge
2. Mortality in newborns with CCHD
3. Morbidity in newborns with CCHD

3e. Key words

Mesh terms: Oximetry
Heart defects, congenital
Newborn, infant

Svenska sökord: pulsoximetri, hjärtmissbildning, nyfödd

Review of the Level of Evidence

4. Search strategy, study selection and references – Appendix 3 (Search strategy, Eligibility criteria, Selection process – flow diagram, References)

During October, 2010, the library performed searches in PubMed, The Cochrane Library, CINAHL, EMBASE and a number of HTA-databases (see Appendix 3 for details). Reference lists of relevant articles were also scanned for additional references. A total of 832 articles were identified after removal of duplicates, of which 777 abstracts were excluded by the library. Another 34 articles were excluded after having been read in full text. Twenty-one articles were sent to the whole work group. Nine of these articles have been critically appraised and are included in the report. The appraisal of articles is based on checklists from SBU – Swedish Council on Health Technology Assessment (2008), which were developed by Professor Olle Nyrén, Karolinska Institutet, Stockholm.

Search strategies, eligibility criteria and a graphic presentation of the selection process together with reference lists are presented in Appendix 3. All searches were made by two librarians (ELD and AL).

5a. Describe briefly the present knowledge of the health technology

The systematic literature search identified eight studies (nine articles) that fulfilled the selection criteria. One study was presented in two articles (Meberg, 2008, Meberg, 2009). All the studies evaluated the diagnostic accuracy of POX screening with echocardiography as reference standard. Two of the studies were also comparative and included a control group without POX screening (Meberg 2009, de-Wahl Granelli, 2009). There were no randomised controlled trials.

The main features of each study, the inclusion and the exclusion criteria and the test characteristics are presented in Table 1, Appendix 1. POX screening was performed on asymptomatic newborns in all studies. Five of them excluded newborns that were prenatally diagnosed with CHD (de-Wahl Granelli 2009, Meberg 2008, 2009, Koppel 2003, Riede 2010, Rosati 2005). A cut-off level of saturation below 95% was used in most studies. The age at the time of the first POX measurement varied from four to over 72 hours after birth.

There was a lack of blinding for the reference standard assessment (echocardiography) in all studies. Newborns with low oxygen saturation underwent echocardiography. Newborns with normal oxygen saturation had a physical examination as follow up. Some studies used data from cardiology clinics or malformation registries as additional follow up.

Studies were evaluated according to a standardised protocol for diagnostic and observational studies. The methodological quality of the studies is presented in Table 1, Appendix 1.

Primary outcome: Diagnostic accuracy

Pulse oximetry screening and physical examination

Four trials evaluated the accuracy of POX screening combined with newborn physical examination for diagnosing CCHD (Table 2a, Appendix 1). One study was of high quality, two studies were of moderate and one study was of low quality. The sensitivity for POX and physical examination to detect CCHD varied from 60% (95% CI 23-88) to 89% (95% CI 72-96). The specificity varied from 98% (95% CI 98-98) to 100% (95% CI 100-100). The false positive rate for CCHD was 0.01-2.1%.

Pulse oximetry screening alone

Seven trials evaluated the accuracy of POX screening alone for CCHD (Table 2b, Appendix 1). One study was of high quality, three were of moderate and three were of low quality. The sensitivity for POX to detect CCHD varied from 62% (95% CI 44-77) to 97% (95% CI 76-100). The specificity varied from 94% (95% CI 94-95) to 100% (95% CI % 100-100). The false positive rate for CCHD was 0.04-5.6%. Among newborns with a reported “false” positive POX some other pathology was reported in 45%-70% (see footnote in Table 2b).

Physical examination alone

One study of high quality evaluated the accuracy of newborn physical examination alone for diagnosing CCHD (Table 2c, Appendix 1). The sensitivity was 62.5% (95% CI 39-82), and the specificity was 98.1% (95% CI 98-98). The false positive rate was 1.9%.

Summary of evidence

POX combined with physical examination or POX alone has a good diagnostic accuracy to detect CCHD. The level of evidence is moderate (according to SBU’s previous system). Furthermore, the results from two studies (of high and moderate quality, respectively) indicate that the combined screening with POX and physical examination has better diagnostic accuracy (sensitivity 83-89%, specificity 98-99%) than POX screening alone (sensitivity 62-77%, specificity 99-100%) or merely screening with physical examination alone (sensitivity 62%, specificity 98%). No statistical analysis was performed.

The negative predictive value was 100% in all three comparisons.

Secondary outcomes

Two prospective observational cohort studies evaluated POX and physical examination versus physical examination alone for undetected CCHD before discharge and mortality from CCHD (Meberg, 2009 (moderate to low quality), de-Wahl Granelli, 2009 (moderate quality)) (Table 3 a, b, Appendix 1). One of them assessed severe acidosis as a marker of morbidity (Table 3c, Appendix 1).

Discharge of newborns with undetected CCHD

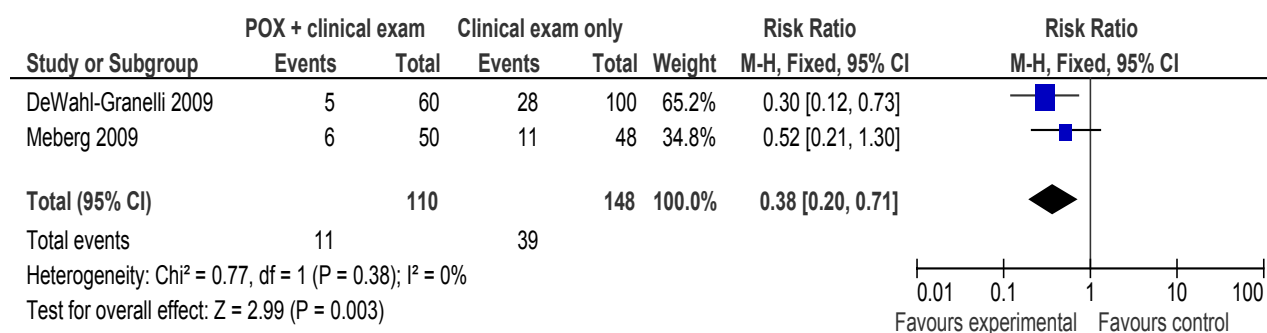
Both trials included data of newborns with undetected CCHD before discharge and their results are presented in Table 3a, Appendix 1.

POX and physical examination versus physical examination alone was associated with a reduced risk for undetected CCHD before discharge (RR 0.38; 95% CI 0.20-0.71). See Figure 2 below.

The level of evidence according to the GRADE system is low (⊕⊕).

Figure 2

Observational cohort studies examining pulse oximetry and physical examination versus physical examination alone. Outcome: Discharge of newborns with undetected critical congenital heart defects



Mortality in newborns with CCHD

There were too few events to evaluate mortality in newborns with CCHD. No deaths occurred in the POX-screened groups (Table 3b).

The level of evidence according to the GRADE system is very low (⊕).

Morbidity (severe acidosis) in newborns with CCHD

POX combined with physical examination was associated with a decreased risk for severe acidosis in newborns with CCHD in comparison with physical examination alone (RR 0.40 (0.20-0.80) (Table 3c).

The level of evidence according to the GRADE system is low (⊕⊕).

5b. Outcome tables – Appendix 1.

Table 1. Study characteristics and quality of the included trials.

Table 2 a-c. Primary outcome: Accuracy of POX screening and physical examination, POX screening alone and physical examination alone for detecting CCHD.

Table 3 a-c. Secondary outcomes: Discharge of newborns with undetected CCHD, mortality and severe acidosis in newborns with CCHD.

5c. Excluded articles – Appendix 2

Excluded articles and reasons for exclusion are presented in Appendix 2

5d. Ongoing research

A multicentre prospective study to assess diagnostic accuracy and cost-effectiveness of routine POX to screen for CHD in newborns is currently ongoing in the UK (Health Technology Assessment, principal investigator Ewer). The aim of the study is to recruit 20 000 newborns to assess test accuracy and parental acceptability. The estimated date of publication according to the study protocol is August 2011.

A search in www.clinicaltrials.gov (2010-10-15) with the keywords (newborn OR "Infant, Newborn" OR neonate OR "newborn infant" OR "newborn baby") AND (pox OR "pulse oximeter" OR "pulse oximetry" OR oximetry OR "oximetry, pulse") identified 24 trials. None of the trials was relevant for the question at issue.

6 Which medical societies or health authorities recommend the new health technology?

A national investigation concerning recommendations of physical examination and screening for various conditions including CHD of newborns before discharge from the well baby nursery is ongoing (Swedish Pediatric Society, Division of Neonatology).

Ethical aspects

7a. Ethical consequences

A general view is that POX screening for CCHD is well accepted by parents since it is simple and accurate, and does not cause any discomfort for their baby. As with other screening methods it is important that the parents are well informed about the purpose of the test as well as its limitations. It is also important that the test is accurately performed and that the results are handled properly.

A false-negative test result may lead to a delay in diagnosis since the health care professionals will be reassured by the negative result and, therefore, may be less responsive to parental concerns. Parents may then have future difficulties to rely on health care professionals, particularly if their baby suffers sequelae that are directly related to the delay in the diagnosis.

False-positive test results may cause unnecessary parental concerns. In these instances it is important that the parents receive adequate information by experienced health care professionals and that echocardiography is performed without any delay. The costs generated by false positive results should also be considered.

Uniform pre- and postnatal screening routines are desirable nationwide in Sweden. This will assure equal health care and a sense of security for parents.

The psychosocial effects of POX screening on parents have not yet been evaluated.

7b. Will other patient groups or other treatments be adversely affected (pushed aside) due to an introduction of the new health technology?

POX screening is a complementary tool to enable the detection of CCHD. It should not replace the physical examination of the newborn.

To avoid negative consequences for the obstetric and pediatric care, the additional costs must be accounted for.

It is also important to realize that POX screening may lead to earlier diagnosis of newborns with other neonatal morbidity (i.e. lung problems or infections) that also may have low POX-values. This would mean an additional secondary benefit of the POX screening (footnote, Table 2b, Appendix 1).

Organisation

8a. When can this new health technology be put into practice?

We estimate that POX screening of newborns could become a clinical routine at Sahlgrenska University Hospital approximately six months after decision, (i.e. the time used for planning and education of personnel).

8b. Is this technology used in other hospitals in Western Region of Sweden?

Screening of newborns with POX is presently in use in Trollhättan (NÄL) and Borås (SÄS) but not in Skövde (SKAS) or in Göteborg (Sahlgrenska University Hospital, Östra and Mölndal).

8c. According to the work group, will there be any consequences from use of the new health technology for personnel?

The POX screening is mainly performed by a nurses' aid. The introduction of a general screening programme of 11 000 newborns per year requires some education and training of the medical staff. An abnormal test result or a technical problem will increase the workload for personnel to some extent.

8d. Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

False positive screening results (22/year in Göteborg) will generate additional physical examinations of newborns as well as pediatric cardiology consultations including echocardiography.

Economy

9a. Present costs of currently used technologies.

The physical examination of newborns is already part of the clinical routine and the associated costs are integrated in the pediatricians' wages. No additional costs concerning the physical examination are expected.

9b. Expected costs of the new health technology

The total cost of POX, calculated per 11 000 screened newborns at Sahlgrenska University Hospital per year:

| | |
|--|-------------|
| Estimated time/ examination: 15 min; 2750 h, 1.4 nurses' aid / year | |
| Staff: 1.4 nurses' aid / year, 1.4 x 400.000 | 560.000 SEK |
| Equipment: POX machine: 3x 20.000 | |
| (three new machines needed to have one machine per ward): | 60.000 SEK |
| Room: | 10.000 SEK |
| Training/education of staff: 3 months: | 100.000 SEK |
| Echocardiography: 0.2% (2.1-1.9%) x 11 000= 22/year | |
| (False positive rate POX and physical examination vs physical examination alone (de-Wahl Granelli, 2009): 22 x 2500 SEK) | 55.000 SEK |
| Neonatal physical examination: 0.2% (2.1-1.9%) x 11 000= 22/year (22 x 500 SEK) | 11.000 SEK |
| <hr/> | |
| Total: | 796.000 SEK |

The cost per timely diagnosis:

| | |
|------------------------------|------------------------|
| First year: 796.000/3* | 265.000 SEK (€ 29.400) |
| After first year: 636.000/3* | 212.000 SEK (€ 23.600) |

* Number of newborns with timely diagnosis (see 3b)

9c. Total change of cost

Our calculation above (9 b) is based on an estimated time necessary for each examination of 15 minutes. If this time could be reduced to 10 minutes, the cost per timely diagnosis after the first year of screening will be reduced to 152.000 SEK (€ 16.900). Reduced cost for the pediatric intensive care would potentially balance the cost for the POX screening. See also 9e.

9d. Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

Our estimated cost presented above (9 b) with an annual total cost of approximately 800.000 SEK cannot be adopted within the present budget.

**9e. Are there any available analyses of health economy?
Cost advantages or disadvantages?**

Two studies of cost-effectiveness were available. According to a British study the additional cost for timely diagnosis of life threatening CHD was £4,894 for pulse oximetry combined with physical examination compared to clinical examination alone (incremental cost-effectiveness, calculated per 100,000 live births, 2000/2001 prices) (Griebsch, 2007). In this analysis the estimated time needed for a POX screening examination was two minutes per newborn. The authors did not seem to consider any time for information to the parents or preparations for the test. The authors concluded that adding POX to clinical examination is likely to be a cost-effective newborn screening strategy for CHD, but further research was required before this policy could be recommended.

The study performed at Sahlgrenska University Hospital during 2004 to 2007 included a cost benefit analysis (de-Wahl Granelli, 2009). However, the calculation and the estimated time required performing a POX examination was not reported in the Swedish study, but the authors referred to the study by Griebsch et al. (Griebsch, 2007).

| |
|-----------------------------|
| Unanswered Questions |
|-----------------------------|

10a. Important gaps in scientific knowledge?

There is still a lack of randomized controlled trials to evaluate POX as a screening tool in newborns.

The postnatal consequences of prenatal fetal cardiac screening are presently unknown. With improved techniques it may lead to an increased detection of CHD already during pregnancy, and consequently more terminations of pregnancies and more identified CHD at birth. This would then reduce, or even eliminate, the need for POX screening.

Development and evaluation of the POX technique with different probe locations, i.e. postductally or pre- and postductally, number of screening tests and timing of the test is needed. Furthermore, development of screening techniques that may increase the detection rate of left heart obstructive diseases are needed (i.e. peripheral perfusion index test).

10b. Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

No, not at the present time.

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Puls oxymetri (POX) screening för upptäckt av medfödda hjärtfel hos nyfödda.

Frågeställning:

Leder screening med puls oxymetri (POX), som enskild metod eller i kombination med barnläkarundersökning, av alla nyfödda asymptomatiska barn före hemgång från BB till att fler barn med allvarliga medfödda hjärtmissbildningar upptäcks innan debut av svår sjukdom och till minskad mortalitet och morbiditet jämfört med enbart barnläkarundersökning ?

PICO: (Patient, Intervention, Comparison, Outcome)

P = Nyfödda, asymptomatiska barn

I₁ = POX, oavsett mätprobens lokalisation, i kombination med barnläkarundersökning, vid någon tidpunkt innan hemgång från BB

I₂ = POX under samma förutsättningar, men ingen barnläkarundersökning

C = Barnläkarundersökning

O = Primärt utfall

Sensitivitet och specificitet att identifiera allvarlig hjärtmissbildning verifierad med ekokardiografi

Sekundära utfall

1. Missad diagnos av allvarlig hjärtmissbildning.
2. Mortalitet hos nyfödda med allvarlig hjärtmissbildning.
3. Morbiditet hos nyfödda med allvarlig hjärtmissbildning.

Resultatet av HTA-processen:

Metod och målgrupp:

Medfödda hjärtfel orsakar 6-10 % av all barnadödlighet. Incidensen uppskattas till 8-12/1000 levande födda barn. Allvarliga hjärtmissbildningar där cirkulationen är beroende av en öppetstående ductus arteriosus är potentiellt akut livshotande. Det är mycket angeläget att identifiera dessa tidigt. En tidig hemgång från BB innebär en ökad risk för att ductus arteriosus sluts först när barnet inte längre är kvar på sjukhus med risk för syrebrist, acidosis, allvarlig hjärtsvikt och cirkulatorisk kollaps. Tidig diagnos av allvarliga hjärtmissbildningar, dvs. innan hemgång, är därför av yttersta vikt. För närvarande undersöks alla nyfödda barn på BB av barnläkare. Vid misstanke om ett hjärtfel utreds barnet vidare med ekokardiografi.

Pulsoxymetri (POX) är en icke-invasiv metod att mäta syrgasmättnad. 28 % av alla nyfödda barn med en allvarlig hjärtmissbildning och en duktusberoende cirkulation skrivs ut odiagnostiserade från svenska BB som inte använder POX-screening. POX-screening avser att identifiera nyfödda med en allvarlig hjärtmissbildning redan på sjukhuset, innan cirkulatorisk kollaps inträffar.

Evidensläge

Den systematiska litteratursökningen identifierade åtta diagnostiska studier (nio artiklar). Studiekvaliteten varierade från låg till hög. Två av dessa studerade även kliniska utfall såsom utskrivning med odiagnostiserad allvarlig hjärtsjukdom (medelhög studiekvalitet), mortalitet (låg kvalitet) och morbiditet (medelhög kvalitet). Evidensgraden för kohortstudier med kliniska utfall bedömdes enligt GRADE-systemet och för diagnostiska studier enligt SBU's tidigare evidensgraderingsystem.

Diagnostisk tillförlitlighet

POX kombinerat med barnläkarundersökning eller POX ensamt hade båda en god diagnostisk förmåga att identifiera allvarlig hjärtmissbildning. Det vetenskapliga underlaget bedöms vara måttligt starkt. Jämförande analys av metodernas diagnostiska tillförlitlighet saknas. Resultatet från två studier (av hög respektive medelhög kvalitet) indikerar att kombinationen av POX och barnläkarundersökning har en bättre diskrimineringsförmåga (sensitivitet 83-89%, specificitet 98-99%) än enbart POX (sensitivitet 62-77%, specificitet 99-100%) eller enbart barnläkarundersökning (sensitivitet 62%, specificitet 98%).

Missad diagnos av allvarlig hjärtmissbildning

POX i kombination med barnläkarundersökning var associerat med en lägre risk för att en allvarlig hjärtmissbildning var odiagnosticerad innan hemgång jämfört med enbart barnläkarundersökning (RR 0.38; 95% KI 0.20-0.71). Det vetenskapliga underlaget bedöms vara begränsat (GRADE ⊕⊕).

Mortalitet hos nyfödda med allvarlig hjärtmissbildning

Inga dödsfall inträffade i grupper som genomgått POX-screening, men det totala antalet dödsfall i studierna var för lågt för att kunna värdera effekten på mortalitet. Det vetenskapliga underlaget är otillräckligt (GRADE ⊕).

Morbiditet (svår acidosis) hos nyfödda med allvarlig hjärtmissbildning

POX kombinerat med barnläkarundersökning var associerat med en lägre risk för svår acidosis hos nyfödda med allvarlig hjärtmissbildning jämfört med enbart barnläkarundersökning (RR 0.40; 95% KI 0.20-0.80). Det vetenskapliga underlaget bedöms vara begränsat (GRADE ⊕⊕).

Etiska aspekter:

Det är viktigt föräldrarna är välinformerade om syftet med POX-screening liksom om dess begränsningar. Ett falskt negativt resultat kan medföra en försenad diagnos. Falskt positiva resultat kan medföra onödig oro hos föräldrarna samt onödig utredning som är resurskrävande.

Ekonomiska aspekter

Kostnaden per diagnos ställd i tid dvs. innan hemgång från BB, uppskattas till 265 000 SEK under det första året och därefter en årlig kostnad på 212 000 SEK. Beräkningen är baserad på antagandet att POX-screening kommer att leda till att tre nyfödda barn med allvarlig hjärtmissbildning diagnosticeras per år vid Sahlgrenska Universitetssjukhuset.

Tidigare studier har presenterat resultat där användningen av POX-screening skulle vara kostnadsneutral. Dessa studier har dock inte tagit hänsyn till den tid som krävs för information till föräldrarna samt den tid som behövdes för förberedelser att genomföra testet.

Sammanfattning och slutsats

POX-screening är en icke-invasiv enkel metod med god diagnostisk förmåga att upptäcka allvarliga hjärtmissbildningar hos nyfödda barn innan hemgång från BB. Studier indikerar att kombinationen av POX och barnläkarundersökning har en bättre diskrimineringsförmåga än enbart POX eller barnläkarundersökning. Det vetenskapliga underlaget är fortfarande otillräckligt för att bedöma hur mortalitet och morbiditet påverkas. Kostnader för en introduktion av metoden vid Sahlgrenska Universitetssjukhuset uppskattas till ca 800 000 under det första året, därefter något lägre.

För HTA-kvalitetssäkringsgruppen 2011-04-06

Christina Bergh
Ordförande

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Denna HTA har genomförts på begäran av Ulla Britt Wennerholm, överläkare, verksamhetschef Sahlgrenska Universitetssjukhuset (SU)/ Östra sjukhuset. En arbetsgrupp har utsetts bestående av Ola Hafström, överläkare, verksamhet Neonatologi, och Anastasia Fassoulas, ST-läkare, verksamhet Kardiologi, båda SU/Östra sjukhuset. Från HTA-centrum har Annika Strandell, docent, Ola Samuelsson, docent, Eva-Lotte Daxberg, bibliotekarie samt Ann Liljegren, bibliotekarie varit resurspersoner. HTA-rapporten och åberopad och förtecknad litteratur har sedan granskats av Maria Svensson, överläkare, Njurmedicinska kliniken SU/Sahlgrenska sjukhuset samt Maria Browall, Klinisk Universitetslektor, Fil Dr., Högskolan i Skövde, Institutionen för vård och natur, Skövde
Slutsatser har diskuterats vid möten mellan HTA-centrum och HTA-projektgruppen. Ett utlåtande har tagits fram, diskuterats och fastställts vid HTA-kvalitetssäkringsgruppens möte 2011-04-06. Frågan nominerades 2010-04-21. Projektet har pågått under perioden 2010-09-22 – 2011-04-06. Sista uppdatering av litteratursökning oktober 2010.

Statement from the Regional HTA Centre of the Western Region in Sweden

The Regional Health Technology Assessment Centre (HTA-centre) of the Western Region in Sweden (Region Västra Götaland, VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report.

Pulse oximetry (POX) screening for congenital heart defects in newbornsQuestion at issue:

Does pulse oximetry (POX) screening alone, or in addition to physical examination, of asymptomatic newborns before discharge from the well baby nursery lead to increased detection of critical congenital heart disease (CCHD) and to reduced mortality and morbidity?

PICO: (Patient, Intervention, Comparison, Outcome)

P = Asymptomatic newborns

I₁ = POX, regardless of location of the pulse oximeter probe, combined with physical examination of the newborn at any age before discharge from the well baby nursery

I₂ = POX under the same conditions, but with no physical examination

C = Physical examination

O = Primary outcome: Sensitivity and specificity in detecting CCHD using echocardiography as reference standard

Secondary outcomes:

1. Undetected CCHD at discharge
2. Mortality in newborns with CCHD
3. Morbidity in newborns with CCHD

Summary of the health technology assessment:Method and patient category

Congenital heart defects account for about 6-10% of all infant deaths. The incidence is estimated to be 8-12 per 1000 live births. *Critical* congenital heart defects (CCHD), i.e. hearts with circulation that are dependent on an open ductus arteriosus, are potentially life threatening and pose a particular challenge for early diagnosis. Discharge of a newborn with undiagnosed CCHD with subsequent ductal closure at home may lead to severe consequences with hypoxia, acidosis, severe heart failure, and even circulatory collapse. Therefore a timely diagnosis of CCHD is of utmost importance. Presently, all newborns are screened for CHD by physical examination in the well baby nursery. Infants with positive findings undergo further diagnostic evaluation with echocardiography.

Pulse oximetry (POX) is a non-invasive method to measure oxygen saturation. Currently 28% of all newborns with CCHD and duct dependent circulation are discharged undiagnosed from well baby nurseries in Sweden, which do not use POX screening. The rationale for screening of newborns with POX is early identification of newborns with CCHD already in the hospital before severe circulatory complications occur.

Level of evidence

The systematic literature search identified eight studies (nine articles), which have evaluated the diagnostic accuracy of POX screening. The scientific quality ranged from low to high. Two studies also evaluated the clinical outcomes discharge with undetected CCHD (moderate quality), mortality (low quality) and morbidity (moderate quality). The level of evidence was evaluated according to the GRADE system for cohort studies with clinical outcomes, and according to SBU's previous system for diagnostic accuracy studies.

Diagnostic accuracy

The level of evidence in support of good diagnostic accuracy of POX screening combined with physical examination or POX screening alone to detect CCHD is moderate. Furthermore, the outcome in two studies (of high and moderate quality, respectively) indicates that the combined screening with POX and physical examination has better diagnostic accuracy (sensitivity 83-89%, specificity 98-99%) than POX screening alone (sensitivity 62-77%, specificity 99-100%) or merely screening with physical examination alone (sensitivity 62%, specificity 98%).

Discharge of newborns with undetected CCHD

POX screening combined with physical examination was associated with a reduced risk of undetected CCHD before discharge (RR 0.38; 95% CI 0.20-0.71) in comparison with physical examination alone. Low level of evidence (GRADE ⊕⊕).

Mortality in newborns with CCHD

There were too few events to evaluate mortality in newborns with CCHD. No deaths occurred in the POX-screened groups. Very low level of evidence (GRADE ⊕).

Morbidity (severe acidosis) in newborns with CCHD

POX screening combined with physical examination was associated with a reduced risk of severe acidosis in newborns with CCHD in comparison with physical examination alone (RR 0.40 (0.20-0.80)). Low level of evidence (GRADE ⊕⊕).

Ethical aspects

It is important that parents are well informed about the purpose of a screening test as well as its limitations. A false-negative test result may lead to a delayed diagnosis since the health care professionals may be incorrectly reassured by the negative result, and, therefore, may be less responsive to parental concerns. On the other hand, a false-positive test result may cause unnecessary parental concerns and unnecessary costly investigations.

Economical aspects

The cost per timely diagnosis is estimated to be 265.000 SEK (€ 29.400) during the first year and at 212.000 SEK (€ 23.600) annually thereafter. The calculation is based on the assumption that POX screening combined with physical examination will detect three infants with CCHD per year at Sahlgrenska University Hospital. In contrast to this estimation, previous publications have reported that the addition of POX screening to physical examination of asymptomatic newborns most likely will be cost-neutral. However, these studies have not considered any time for information to the parents or preparations for the test.

Concluding remarks

POX screening is a simple, non-invasive method with a good diagnostic accuracy to detect CCHD in the asymptomatic newborn before discharge from the well baby nursery. Studies indicate that the combination of POX and physical examination has better diagnostic accuracy than either of the examinations alone. There are still insufficient data to evaluate whether this also will affect mortality and morbidity. The costs associated with an introduction of the method at Sahlgrenska University Hospital are estimated to be around 800.000 SEK during the first year, and thereafter the annual cost will be somewhat lower.

On behalf of HTA-centre Göteborg, Sweden, 2011-04-06

Christina Bergh, Professor, MD.
Head of HTA-centre

Ingemar Tessin, Director, Division of Neonatology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Göteborg, Sweden and Anneli Falk, Director, Division of Obstetrics, Sahlgrenska University Hospital, Göteborg, Sweden, requested the present HTA.

A working group under the chairmanship of Ulla-Britt Wennerholm, MD, PhD, Associate Professor, Division of Obstetrics, Sahlgrenska University Hospital, Göteborg, Sweden produced the HTA report. The other members of the working group were Anastasia Fassoulas, MD, Pediatrician, Division of Pediatric Cardiology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Göteborg, Sweden and Ola Hafström, MD, PhD, Division of Neonatology, The Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Göteborg, Sweden. The participants from the HTA centre were Annika Strandell, MD, PhD, Associate Professor, Ola Samuelsson MD, PhD, Associate Professor, Eva-Lotte Daxberg, information specialist and Ann Liljegren information specialist.

Maria Browall, RN, PhD, School of Life Sciences, University of Skövde, Skövde Sweden and Maria Svensson, MD, PhD, Dept of Molecular and Clinical Medicine –Nephrology, Sahlgrenska University Hospital, Göteborg, Sweden have critically appraised the report.

The project lasted during the time period September 22, 2010 to April 6, 2011. The question was requested in April 2010. Last search updated in October 2010.

Table 1
Study characteristics of the trials included in the systematic review of accuracy of pulse oximetry (POX) in detecting critical congenital heart disease in asymptomatic newborns

| Author, year of publication, country | Study design | Population/ No of screened newborns | No of newborns with CCHD | Definition | Inclusion criteria | Exclusion criteria | Age at screening | Probe location | Frequency of testing | Cut off for normal % | Control group | Reference | Quality |
|---|--|--|--|---|-----------------------------------|---|---|-----------------------------------|--|---|--|--|--|
| Arlettaz, 2006, Switzerland, 3 clinics | Prospective observational study Consecutive Not blind | 3 663 Screened: 3 262 | 15 | CCHD (CHD of functional consequence or cyanotic (Mitchell definition)) | Healthy newborns ≥ 35 weeks | GA < 35 weeks and infants with resp. disorders | 8 h (6-12) | Right or left foot | Multiple: POX repeated 4-6 h later if 90-94% | Functional ≥ 95 | No | Echo (if POX $< 90\%$ or repeated POX 90-94%) | Low |
| de-Wahl Granelli, 2009, Sweden, 4 clinics in Västra Götaland region | Prospective observational cohort study Consecutive Not blind | 46 963, 39 821 screened with POX and physical exam. (38 429 complete data) | 60 in study group and 100 in control group | CCHD (duct dependent heart disease) | All babies in well baby nurseries | Prenatally diagnosed CHD | Median 38 h (1-406) | Right hand and right or left foot | Multiple: POX repeated 2-3 times if 90-94% | Functional ≥ 95 or difference hand-foot ≤ 3 | 108 604 infants born in referral hospitals not using POX screening | Echo (if POX < 90 or repeated POX 90-94%) + data from the cardiology clinic + Rattsbase (data on deaths) | Diagn. study: High Obs. study: Moderate |
| Koppel, 2003, USA, 2 clinics | Prospective observational study Consecutive Not blind | Screened: 11 281 | 5 | CCHD (likely to require surgery or intervention during first month of life) | Asymptomatic newborns | Symptomatic newborns and prenatally diagnosed CHD | > 24 h or at discharge (mean 56.9 h (VD) or 103.2 h (CS)) | Foot | Single | Functional ≥ 96 | No | Echo (if POX < 96) + data from malformation registry | Low |
| Meberg, 2008, Norway, 14 clinics | Prospective observational study Consecutive Not blind | 57 959 Screened: 50 008 | 35 | CCHD (duct dependent or cyanotic heart disease) | Healthy babies | NICU admissions and prenatally diagnosed CHD | Admitted from delivery ward | Right or left foot | Multiple: POX repeated 2-3 h if $< 95\%$ | ≥ 95 | No | Echo + CHDs in population prospectively registered 6 months after last birth | Moderate |

| Author, year of publication, country | Study design | Population/ No of screened newborns | No of newborns with CCHD | Definition | Inclusion criteria | Exclusion criteria | Age at screening | Probe location | Frequency of testing | Cut off for normal % | Control group | Reference | Quality |
|--|---|---|---|---|---|--|-----------------------------|--|--|----------------------|--|---|--------------|
| Meberg, 2009, Norway, 14 clinics | Prospective observational cohort study Consecutive Not blind | 57 959, 50 008 screened with POX and physical exam. | 50 in study group and 48 in control group | CCHD (duct dependent or cyanotic heart disease) | Healthy babies | NICU admissions and prenatally diagnosed CHD | Admitted from delivery ward | Right or left foot | Multiple: POX repeated 2-3 h if < 95% | ≥95 | 58 098 infants born in hospitals not using POX screening | Echo +CCHDs in population prospectively registered 6 months after last birth. Control group: CCHDs retrospectively registered in hospital databases | Moderate/low |
| Riede, 2010, Germany, 34 clinics | Prospective observational study Consecutive Not blind | 48 348 Screened: 41 445 (3 excl. due to protocol violation) | 18 | CCHD (duct dependent or cyanotic heart disease) | Fullterm (≥37 weeks) and postterm neonates. Normal routine physical exam. | Prenatally diagnosed CHD | 24-72 h | Right or left foot Different devices used | Multiple: POX repeated 1 h later if < 96% | ≥96 | No | Echo + referral follow up | Moderate |
| Rosati, 2005, Italy, one clinic | Prospective observational study Consecutive Not blind | Screened: 5 292 | 3 | CCHD (likely to require surgery or intervention during first month of life) | Term asymptomatic newborns | Symptomatic newborns. Prenatally diagnosed CHD | 72 h | Foot | Single | ≥96 | No | Echo + referral follow up | Low |
| Sendelbach, 2008, Texas, USA, one clinic | Prospective observational study Consecutive Blind at 4h, but not at discharge | 15 299 Screened: 15 233 | 4 | CCHD (duct dependent or cyanotic heart disease) | Term and late preterm ≥35 w, ≥2100g | NICU admissions | 4 h | Right or left foot | Multiple: POX repeated at discharge if < 96% | ≥96 | No | Echo | Moderate |
| Tautz, 2010, Germany, 3 clinics | Prospective observational study Consecutive Not blind | 3 695 Screened: 3 364 | 11 | CCHD (definition unclear) | Term ≥ 35 w | Preterm <35 w or ventilated newborns | 6-36 h | Right or left foot | Multiple: POX repeated 4-6 h later if 90-94% | Functional ≥95 | No | Echo | Low |

CHD congenital heart defects, CCHD critical congenital heart defects, POX pulse oximetry, GA gestational age, VD vaginal delivery, CS caesarean delivery, NICU neonatal intensive care unit.

Table 2a**The accuracy of pulse oximetry (POX) and physical examination in detecting critical congenital heart defects in asymptomatic newborns**

| Author | No of patients | Sensitivity, % (true positive rate) (95% CI) | Specificity, % (true negative rate) (95% CI) | False positive rate (%) |
|------------------------|----------------|--|--|----------------------------|
| de-Wahl Granelli, 2009 | 38 429 | 82.8 (65.5-92.4) | 97.9 (97.7-98.0) | 2.1 |
| Koppel, 2003 | 11 281 | 60.0 (23.1-88.2) | 99.99 (99.99-100) | 0.01 |
| Meberg, 2008 | 50 008 | 88.6 (72.3-96.3) | 99.4 (99.3-99.5) | 0.6 |
| Sendelbach, 2008 | 15 233 | Not estimable | 100 (100-100) | 0.01 |

CI confidence interval

Table 2b**The accuracy of pulse oximetry (POX) screening in detecting critical congenital heart defects in asymptomatic newborns**

| Author | No of patients | Sensitivity, % (true positive rate) (95% CI) | Specificity, % (true negative rate) (95% CI) | False positive rate (%) |
|------------------------|----------------|--|--|----------------------------|
| Arlettaz, 2006 | 3 262 | 96.9 (75.9-99.7) | 99.7 (99.5-99.8) | 0.28 |
| de-Wahl Granelli, 2009 | 38 429 | 62.1 (44.0-77.3) | 99.8 (99.8-99.9) | 0.17* |
| Meberg, 2008 | 50 008 | 77.1 (61.0-87.9) | 99.4 (99.3-99.5) | 0.6** |
| Riede,2010 | 41 445 | 77.8 (54.8-91.0) | 99.99 (99.9-99.9) | 0.10*** |
| Rosati, 2005 | 5 292 | 66.7 (20.8-93.9) | 100 (99.9-100.0) | 0.04 |
| Sendelbach, 2008 | 15 233 | 75.0 (30.1-95.4) | 94.4 (94.0-94.7) | 5.6# |
| Tautz, 2010 | 3 364 | 81.8 (52.3-94.9) | 99.7 (99.5-99.9) | 0.27 |

CI confidence interval

* **de-Wahl Granelli:** False positive 69: other CCHD (n=4), other mild CHD (n=10), persistent pulmonary hypertension (n=6), transitional circulation (n= 8), infection (n=10), pulmonary pathology (n=7), normal (n=24) (other than CHD pathology 31/69).

****Meberg 2008:** False positive 281: Pneumonia/septicemia (n=55), transient tachypnea (n=54), persistent pulmonary hypertension (n=6), pneumothorax (n=6), amniotic fluid aspiration (n=5), miscellaneous (hypoglycemia, pulmonary atelectasis, polycythemia, infantile pulmonary fibromatosis, respiratory distress syndrome, cardiomyopathy (n=8), healthy with transitional circulation (n=147)

*****Riede:** False positive 40: persistent pulmonary hypertension (n=15), sepsis (n=13), normal (n= 12)

screening at 4h of age

Table 2c**The accuracy of physical examination in detecting critical congenital heart defects in asymptomatic newborns**

| Author | No of patients | Sensitivity, % (true positive rate) (95% CI) | Specificity, % (true negative rate) (95% CI) | False positive rate (%) |
|------------------------|----------------|--|--|----------------------------|
| de-Wahl Granelli, 2009 | 38 374 | 62.5 (38.6-81.5) | 98.1 (97.9-98.2) | 1.90 |

CI confidence interval

Table 3a

**Observational cohort studies examining pulse oximetry and physical examination versus physical examination alone.
The risk for a newborn of being discharged from the well baby nursery with undetected critical congenital heart disease.**

| Author, year, country | CCHD in population | Withdrawals-drop outs | Results POX | Results Control group | RR (95% CI) POX vs control group | Comments | Quality |
|--------------------------------|---|---|---|---|---|---|----------|
| Meberg, 2009, Norway | POX group 81/57 959 (1.40/1000) Control group 55/ 58 098 (0.95/1000) | POX: 7959 not screened (14%) | 6*/50 (12%) | 11/48 (23%) | 0.52 (0.21-1.30) p=0.15 p=0.05 (if 2 failures in POX group excluded) | Prenatally CCHD excluded: 31 in POX group, 7 in control group | Low |
| de-Wahl Granelli, 2009, Sweden | POX group: 62/46 963 (1.32/1000) Control group: 109/108604 (1.00/1000) | POX group (18.2%):7064 not eligible and 1470 not screened (refusal=19, POX failure=18, staff shortage=2, incomplete recording of POX =39 or clin exam=1392) | 5/60 (8 %) | 28/100 (28%) | 0.30 (0.12-0.73) p=0.0025 | Prenatally CCHD excluded: 2 in POX group, 9 in control group | Moderate |
| | | | Systemic duct dependent circulation 5/30 (17%) | Systemic duct dependent circulation 16/48 (33%) | 0.50 (0.20-1.22) p=0.12 | | |
| | | | Pulmonary duct dependent circulation 0/30 | Pulmonary duct dependent circulation 12/52 (23%) | 0.07 (0.004-1.12) p=0.0030 | | |

POX pulse oximetry, CCHD critical congenital heart disease

* 2 POX failures, subnormal POX but not referred

Table 3b**Observational studies examining pulse oximetry and physical examination versus physical examination only.
Mortality in newborns with critical congenital heart disease**

| Author, year, country | CCHD in population | Withdrawals-drop outs | Results POX | Results Control group | RR (95% CI) | Comments | Quality |
|--------------------------------|---|---|-------------|-----------------------|-------------------------------|---|---------|
| Meberg, 2009, Norway | POX group 81/57 959 (1.40/1000) Control group 55/ 58 098 (0.95/1000) | POX: 7959 not screened (14%) | 0 | 0 | Not estimable | Prenatally CCHD excluded: 31 in POX group, 7 in control group | Low |
| de-Wahl-Granelli, 2009, Sweden | POX group: 62/46 963 (1.32/1000) Control group: 109/108604 (1.00/1000) | POX group (18.2%):7064 not eligible and 1470 not screened (refusal=19, POX failure=18, staff shortage=2, incomplete recording of POX =39 or clin exam=1392) | 0/60 | 5/100 | 0.15 (0.01-2.68) p=0.16 | Prenatally CCHD excluded: 2 in POX group, 9 in control group | Low |

POX pulse oximetry, CCHD critical congenital heart disease

Table 3c**Observational studies examining pulse oximetry and physical examination versus physical examination only.
Severe acidosis in newborns with critical congenital heart disease.**

| Author, year, country | CCHD in population | Withdrawals-drop outs | Results POX | Results Control group | RR (95% CI) POX vs control group | Comments | Quality |
|--------------------------------|---|---|-------------|-----------------------|----------------------------------|--|---------|
| de-Wahl Granelli, 2009, Sweden | POX group: 62/46 963 (1.32/1000) Control group: 109/108604 (1.00/1000) | POX group (18.2%):7064 not eligible and 1470 not screened (refusal=19, POX failure=18, staff shortage=2, incomplete recording of POX =39 or clin exam=1392) | 7/60 (12%) | 33/100 (33%) | 0.35 (0.17-0.75) p=0.0025 | Prenatally CCHD excluded: 2 in POX group, 9 in control group | Low |

POX pulse oximetry, CCHD critical congenital heart disease

Appendix 2

Excluded articles and reasons for exclusions

| Study (author and year) | Reason for exclusion |
|------------------------------|---|
| Bakr et al, 2005 | Not concurrent with PICO (not CCHD) |
| de-Wahl Granelli et al, 2007 | Intervention (method) not concurrent with PICO |
| Griebsch et al 2007 | Not concurrent with PICO. The article was included in the cost-effectiveness assessment |
| Hoffman, 2011 | No systematic review |
| Knowles et al, 2005 | Systematic review including too old articles |
| Liske et al, 2006 | No systematic review |
| Mahle et al, 2009 | No systematic review |
| Reich et al, 2008 | Inappropriate study design according to PICO |
| Reich et al, 2003 | Insufficient data |
| Thangaratinam et al, 2007 | Systematic review including some too old articles |
| Valmari, 2010 | No systematic review |
| Walsh, 2010 | Poor study design (low participation rate) |

Appendix 3: Search strategy, study selection and references

PICO

What is the diagnostic accuracy for pulse oximetry in screening of asymptomatic newborns before discharge from the well baby nursery and does pulse oximetry screening, alone or in addition to physical examination, lead to increased detection of critical congenital heart disease (CCHD) and reduced mortality and morbidity?

PICO: (Patient, Intervention, Comparison, Outcome)

P = Asymptomatic newborns

I₁ = POX, regardless of location of the pulse oximeter probe, combined with physical examination of the newborn at any age before discharge from the well baby nursery

I₂ = POX under the same conditions, but with no physical examination

C = Physical examination

O = Primary outcome: Sensitivity and specificity in detecting CCHD using echocardiography as reference standard

Secondary outcomes:

1. Undetected CCHD at discharge
2. Mortality in newborns with CCHD
3. Morbidity in newborns with CCHD

Search strategy

PubMed 2010-10-01

newborn OR newborns OR "Infant, Newborn"[Mesh] OR neonate OR neonates OR "newborn babies" OR "newborn infant" OR "newborn infants" OR "newborn baby"

AND

POX OR pulse oximeter OR pulse oximetry OR oximetry

NOT

Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]

Limits: English, Danish, Norwegian, Swedish, Publication Date from 2003

410 results

EMBASE (OVID SP) 2010-10-01

exp newborn/ OR newborn*.af. OR neonat*.af. OR newborn babies.af. OR newborn baby.af. OR newborn infant*.af.

AND

exp oximetry/ OR oximetry.mp. OR pulse oximetry.mp. OR exp pulse oximetry/ OR pulse oximeter.mp. OR exp pulse oximeter/ OR POX.mp.

Limits: English, Danish, Norwegian, Swedish, Publication Date from 2003

558 results

CINAHL (EBSCO) 2010-10-04

(MH "Infant, Newborn+") OR newborn* OR neonat* OR "Newborn babies" OR "newborn baby" OR "newborn infant*"

AND

(MH "Pulse Oximetry") OR pulse oximetry OR (MH "Oximetry+") OR POX OR (MH "Pulse Oximeters") OR pulse oximeter

Limits: English, Danish, Norwegian, Swedish, Publication Date from 2003

311 results

The Cochrane Library 2010-10-01

newborn OR infant, newborn OR newborn infant OR newborn baby OR neonate **in** Title, Abstract or Keywords OR MeSH descriptor Infant, Newborn explode all trees

AND

Pulse oximetry OR pulse oximeter OR Oximetry OR POX **in** Title, Abstract or Keywords OR MeSH descriptor Oximetry explode all trees

Limits: Publication Date from 2003

82 results

Cochrane reviews **4**

Other reviews **1**

Clinical trials **71**

Technology Assessments **1**

Economic evaluations **5**

CRD 2010-10-04

newborn OR newborns OR infant OR infants OR neonate OR neonates OR "newborn baby" OR "newborn babies" OR "newborn infant" OR "newborn infants" OR MeSH Infant, Newborn EXPLODE 1

AND

POX OR MeSH Oximetry EXPLODE 1 2 3 OR "pulse oximetry" OR "pulse oximeter"

Limits: Publication Date from 2003

12 results

SBU, Kunnskapssenteret, Sundhedsstyrelsen 2010-10-01

Nothing new was identified.

Reference lists:

A comprehensive review of reference lists brought no new references.

Eligibility criteria

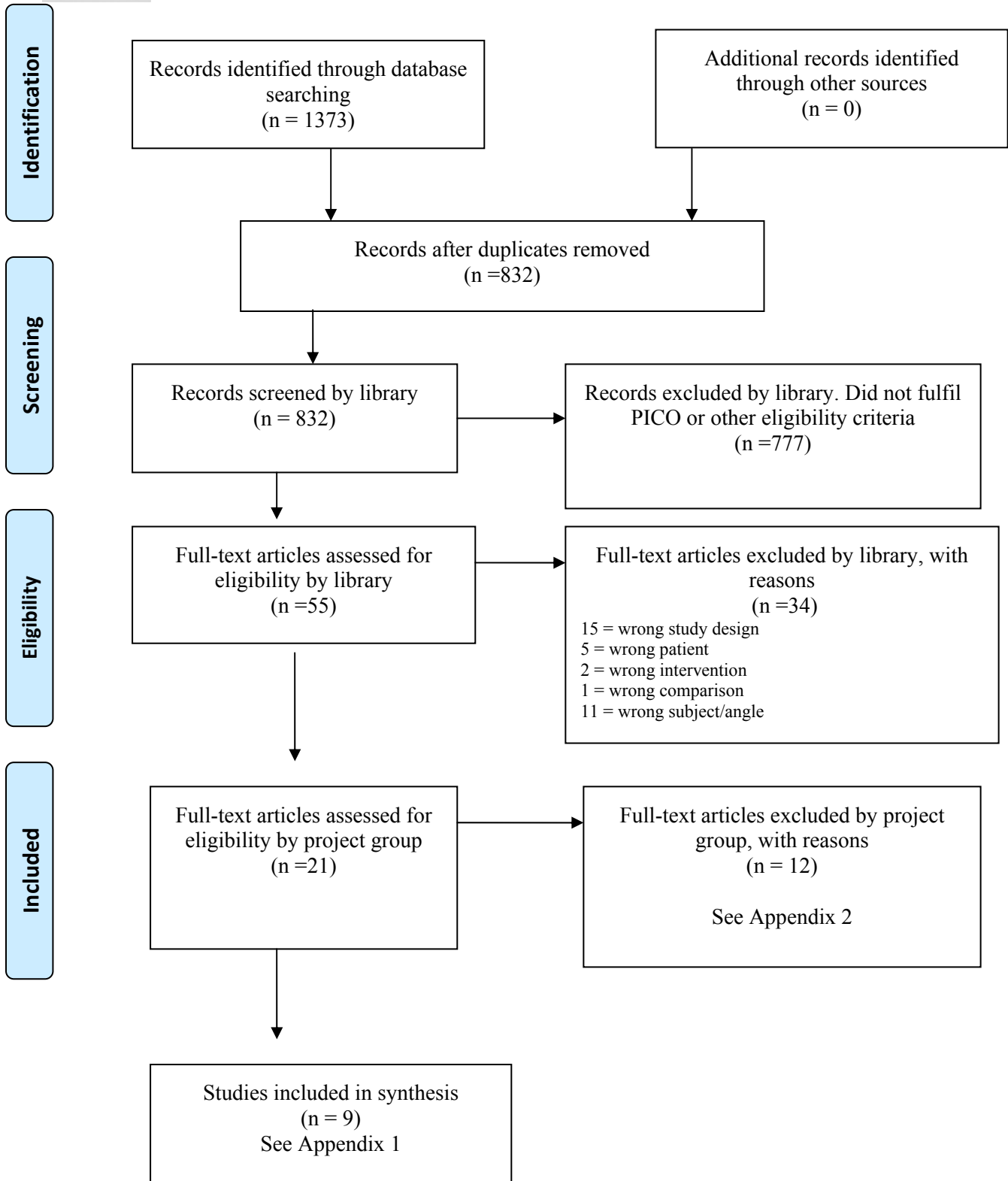
Study design:

- Studies with some kind of control group
- No case reports or review articles

Language: English, Danish, Norwegian, Swedish

Publication date from: 2003

Selection process – flow diagram



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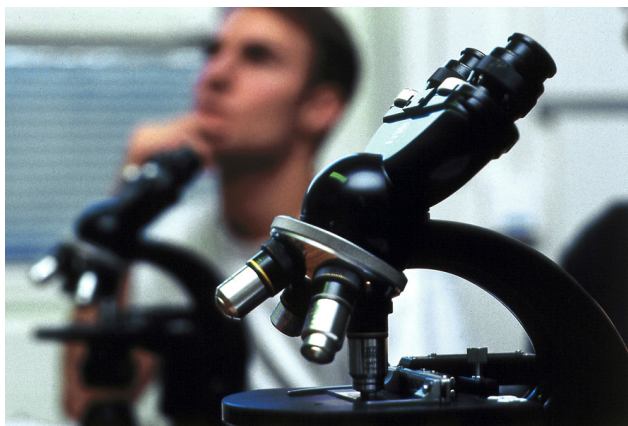
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HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is

currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

| | |
|------------------------------|--------|
| High quality of evidence | = ⊕⊕⊕⊕ |
| Moderate quality of evidence | = ⊕⊕⊕ |
| Low quality of evidence | = ⊕⊕ |
| Very low quality of evidence | = ⊕ |

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

For diagnostic studies, the GRADE system should be applied for clinical outcomes and we have thus chosen not to use it for diagnostic accuracy studies.. In the present report, we have evaluated the level of evidence for diagnostic accuracy according to the system previously used by SBU, (Swedish Council on Health Technology Assessment), briefly described below.

High level of evidence

At least two studies of high quality or a systematic review of good quality

Moderate level of evidence

One study of high quality and at least two studies of moderate quality

Low level of evidence

At least two studies of moderate quality

Very low level of evidence

Only studies of low quality

Christina Bergh, Professor, MD.
Head of HTA-centre

