

Pulse oximetry screening for congenital heart defects in newborn infants (PulseOx): a test accuracy study



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Summary

Background Screening for congenital heart defects relies on antenatal ultrasonography and postnatal clinical examination; however, life-threatening defects often are not detected. We prospectively assessed the accuracy of pulse oximetry as a screening test for congenital heart defects.

Methods In six maternity units in the UK, asymptomatic newborn babies (gestation >34 weeks) were screened with pulse oximetry before discharge. Infants who did not achieve predetermined oxygen saturation thresholds underwent echocardiography. All other infants were followed up to 12 months of age by use of regional and national registries and clinical follow-up. The main outcome was the sensitivity and specificity of pulse oximetry for detection of critical congenital heart defects (causing death or requiring invasive intervention before 28 days) or major congenital heart disease (causing death or requiring invasive intervention within 12 months of age).

Findings 20 055 newborn babies were screened and 53 had major congenital heart disease (24 critical), a prevalence of 2.6 per 1000 livebirths. Analyses were done on all babies for whom a pulse oximetry reading was obtained. Sensitivity of pulse oximetry was 75.00% (95% CI 53.29–90.23) for critical cases and 49.06% (35.06–63.16) for all major congenital heart defects. In 35 cases, congenital heart defects were already suspected after antenatal ultrasonography, and exclusion of these reduced the sensitivity to 58.33% (27.67–84.83) for critical cases and 28.57% (14.64–46.30) for all cases of major congenital heart defects. False-positive results were noted for 169 (0.8%) babies (specificity 99.16%, 99.02–99.28), of which six cases were significant, but not major, congenital heart defects, and 40 were other illnesses that required urgent medical intervention.

Interpretation Pulse oximetry is a safe, feasible test that adds value to existing screening. It identifies cases of critical congenital heart defects that go undetected with antenatal ultrasonography. The early detection of other diseases is an additional advantage.

Funding National Institute for Health Research Health Technology Assessment programme.

Introduction

Congenital heart defects are the most common group of congenital malformations and a leading cause of infant deaths in the developed world.^{1–4} Early detection of major congenital heart defects (ie, those leading to death or requiring invasive intervention before 1 year of age) might improve the outcome of newborn babies.⁵ Improvement with early detection is particularly true for critical, duct-dependent lesions in which closure of the ductus arteriosus can result in acute cardiovascular collapse, acidosis, and death.^{6–8} Screening for congenital heart defects relies on mid-trimester ultrasound scan in which the fetal heart chambers (preferably including the outflow tracts) are imaged, and postnatal physical examination that includes assessment of pulses and heart sounds and inspection for cyanosis. Both screening methods have a fairly low detection rate and a substantial number of babies are discharged from hospital before congenital heart defects are diagnosed.^{9–13} Some of these babies die or present in such a poor clinical state that the outcome, despite treatment, is compromised.

Pulse oximetry is a well established, accurate, non-invasive test for objective quantification of hypoxaemia.

Use of this screening method for early detection of congenital heart defects is based on the rationale that clinically undetectable hypoxaemia is present, to some degree, in most potentially life-threatening cases. Pulse oximetry has been assessed as a screening method for congenital heart defects in newborn babies in many studies.^{14–25}

The results of a systematic review²⁶ in 2007 drew attention to the difficulties in the assessment of the accuracy of pulse oximetry because of methodological variations, particularly patient selection, timing of measurement, cutoffs for a positive result, types of congenital heart defects screened for, rigour of follow-up, and type of oximeters used. Additionally, most studies were fairly small with low prevalence of congenital heart defects, particularly with the exclusion of patients with antenatally suspected congenital heart defects. Calculation of a priori sample size was not undertaken in any study, and the sample size was often inadequate to estimate sensitivity precisely. Since this review, four more studies have been reported,^{21–23,25} however, up to now, more than 10 000 patients were recruited in only five studies,^{17,21–23,25} and a priori sample

Published Online

August 5, 2011

DOI:10.1016/S0140-6736(11)60753-8

See Online/Comment

DOI:10.1016/S0140-6736(11)61032-5

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size calculations were not done for any of these studies and the effects of previous antenatal screening on the results of pulse oximetry were not assessed.

We assessed the accuracy of pulse oximetry for screening major congenital heart defects in newborn babies, and the contribution of this method after antenatal screening with ultrasonography.

Methods

Study population

Newborn infants were recruited prospectively, and studied according to methods stated in the protocol. In six obstetric units in the West Midlands, UK, all consecutive asymptomatic newborn babies (gestation >34 weeks) were eligible, including newborn babies in whom congenital heart defects were suspected

For the protocol see <http://www.pulseox.bham.ac.uk>

antenatally after midtrimester ultrasonography. These units serve a socioeconomically and ethnically diverse population and represent the range of obstetric settings, from busy district general hospitals to specialised tertiary referral centres. Babies with symptoms suggestive of cardiac disease that were detected before screening were excluded.

The policies and standards of the UK Newborn Screening Programme were adopted. Trent Research Ethics Committee (reference 07/MRE04/40) and NHS Trust research governance approval was obtained for the study. All pregnant women in the centres were provided with study details, and written informed consent was obtained from those who agreed to participate.

Index test

We used the Radical-7 pulse oximeter with the reusable probe LNOP Y1 (Masimo, Irvine, CA, USA). These devices have low intraobserver and interobserver variability¹⁹ and produce accurate saturations that are stable in active individuals and in low perfusion states, making them suitable for use in the first few hours of a newborn baby's life. We measured functional saturations in the right hand and either foot in a non-specified order while the baby was still in hospital. The sensor was secured around the palm of the baby's hand and sole of the foot with a bespoke disposable wrap. Midwives or health-care assistants with appropriate training undertook the tests. Masking of antenatal findings (eg, suspected abnormalities of cardiac anatomy) was not undertaken because pulse oximetry is an objective test and the reading is unlikely to be affected by knowledge of such findings.

A saturation of less than 95% in either limb or a difference of more than 2% between the limb saturation readings (if both were ≥95%) was judged to be abnormal. These threshold values were chosen to try to increase the sensitivity for detection of left heart obstructive lesions, treatable disorders that were missed most often in studies with higher thresholds.

Clinical examination was expedited if an abnormal test result was obtained. If this examination was unremarkable, oximetry was repeated 1–2 h later. If abnormalities of the cardiovascular system were detected with expedited examination, or saturations remained abnormal during a second test, the newborn babies were classified as test positive and echocardiography was undertaken (figure 1).

Reference standard

A composite reference standard, consisting of echocardiography and follow-up, was used to identify immediate and late-presenting cases of congenital heart defects. In test-positive babies, the echocardiography result was classified into one of five groups (panel 1). All babies were followed up through use of regional and national registries. 12 months after recruitment was stopped, cardiac abnormalities were identified by use of the congenital anomalies registers and mortality registers

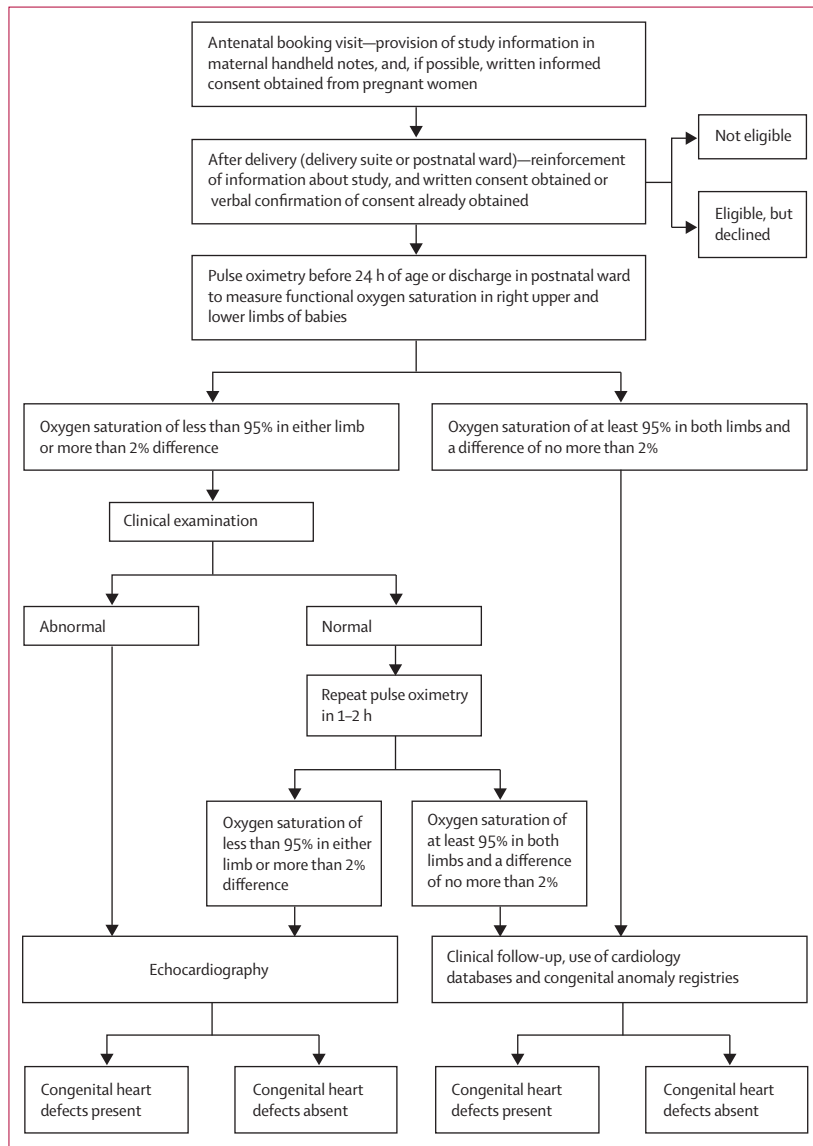


Figure 1: Study design

Panel 1: Definitions of echocardiographic findings**Normal**

No echocardiographic abnormalities.

Non-significant

No clinical signs (eg, murmur, thrill, pulse abnormalities, hepatic enlargement). Presence of any one of small patent ductus arteriosus, small interatrial communication (patent foramen ovale or atrial septal defect), muscular ventricular septal defect, or mildly abnormal turbulence at branch pulmonary artery at birth, and these findings are not detected after 6 months.

Significant

Presence of one of small patent ductus arteriosus, patent foramen ovale, muscular ventricular septal defect, or mildly abnormal turbulence at branch pulmonary artery at birth, and findings persist for longer than 6 months of age. Also any cardiac lesion that requires regular monitoring after 6 months or drug treatment, but is not classified as serious or critical.

Serious

Any cardiac lesion that is not defined as critical, but which requires intervention (cardiac catheterisation or surgery) within 1 year of age.

Critical

All infants with hypoplastic left heart, pulmonary atresia with intact ventricular septum, simple transposition of the great arteries, or interruption of the aortic arch. All infants dying or requiring surgery within the first 28 days of life with coarctation of the aorta, aortic valve stenosis, pulmonary valve stenosis, tetralogy of Fallot, pulmonary atresia with ventricular septal defect, or total anomalous pulmonary venous connection.

for the West Midlands and surrounding regions. Birmingham Children's Hospital paediatric cardiology database (HeartSuite) and the national Central Cardiac Audit Database were also used to identify all cases of congenital heart defects that needed intervention within 1 year (ie, major congenital heart defects).

Statistical analysis

The main outcome was the accuracy (sensitivity and specificity) of detection of major congenital heart defects, subgrouped into critical (ie, death or requiring invasive intervention before 28 days) and major congenital heart disease (ie, death or requiring invasive intervention before 12 months of age). The sample size was calculated by use of simulation with estimates from our systematic review of pulse oximetry.²⁶ Based on a prevalence of congenital heart defects of two per 1000, for an assumed sensitivity of 75% and specificity of 99·5%, a sample size of 20000 babies provided 80% power to prove the sensitivity was at least 52% and more than 90% power to prove the specificity was greater than 99·3% (both by use of a one-sided $\alpha=2\cdot5\%$).

Participants recruited

Participants recruited	
Mothers (n=19 796)*	
Age (years)	
<20	1467 (7%)
20–24	4495 (23%)
25–29	5773 (29%)
30–34	4713 (24%)
35–39	2703 (14%)
≥40	645 (3%)
Ethnic origin	
White	11 003 (56%)
Asian	4902 (25%)
Black	1304 (7%)
Other	1535 (8%)
Not given or missing	1052 (5%)
Gravidity†	
1	7406 (37%)
2	5645 (29%)
3	3228 (16%)
4	1679 (8%)
≥5	1837 (9%)
Missing	1 (<1%)
Parity‡	
1	9163 (46%)
2	5690 (29%)
3	2777 (14%)
≥4	2166 (11%)
Newborn babies (n=20 055)	
Gestational age (weeks)	
35–36	731 (4%)
37–38	4396 (22%)
39–40	11 029 (55%)
>40	3899 (19%)
Sex	
Female	9874 (49%)
Male	10 181 (51%)
Weight (kg; mean, SD)	3·33 (0·52)
Number of twins	518 (3%)

Data are number (%) or mean (SD). *19 537 mothers had singleton births and 259 had twins. †Including current pregnancy.

Table 1: Characteristics of mothers and babies

For the analysis, two cohorts were defined. The first cohort was all recruited babies, and the second excluded those with congenital heart defects that were suspected antenatally. The rationale for the second cohort was to identify babies for whom a positive result with pulse oximetry could make a difference to subsequent testing and contingent health care.

We assessed the diagnostic accuracy for the cohorts by calculating the sensitivity, specificity, and predictive values for critical cases alone and all major cases. 95% CIs for each estimate were calculated by use of binomial exact methods.²⁷ The accuracy of anomaly scans alone was

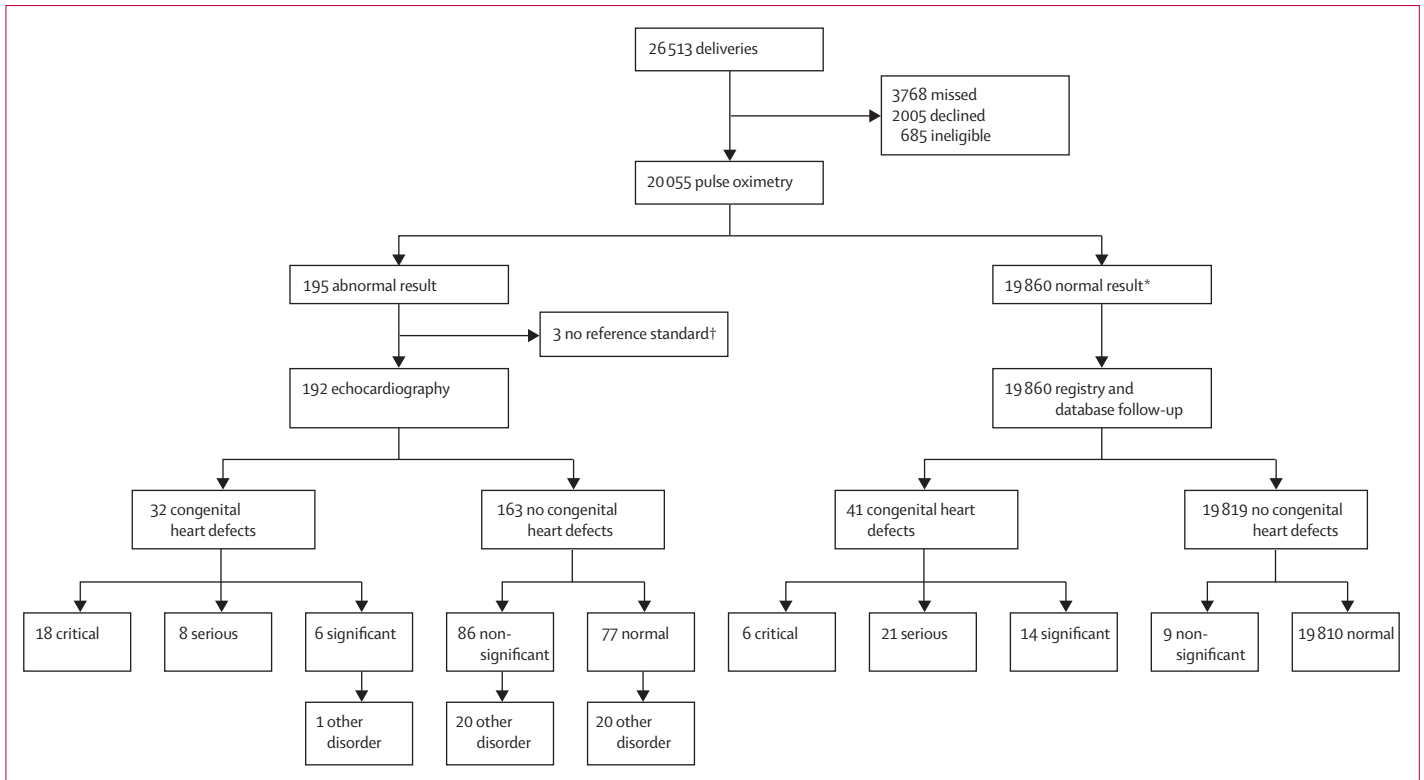


Figure 2: Trial profile

*Includes 78 babies who missed some or all stages of the index test after the first stage of pulse oximetry; these were followed up as per reference standard for normal result and have been confirmed as having no congenital heart defects. †Followed up as per reference standard for normal result and have been confirmed as having no congenital heart defects.

assessed in a similar way. The accuracy of pulse oximetry according to the timing of the test was assessed with a logistic regression model allowing for time from birth to the first stage of pulse oximetry as a continuous variable. This analysis was undertaken separately in babies diagnosed with major congenital heart defects (for sensitivity) and those without (for specificity).

Role of the funding source

The Health Technology Assessment programme monitored study progress but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Table 1 shows the characteristics of the babies and mothers. 20,055 newborn babies were screened between February, 2008, and January, 2009. 195 (0.8%) babies had abnormal results for congenital heart defects according to pulse oximetry and 192 (98%) of these had the reference-standard echocardiography (figure 2). The index test and echocardiography were done within 72 h of each other. Two babies did not have echocardiography, and the tape of the echocardiography result was lost for

one baby and therefore the provisional normal echocardiographic diagnosis could not be ratified. These three babies were followed up through use of clinical databases, and showed no evidence of congenital heart defects and were judged to be false positives.

53 newborn babies were diagnosed with major congenital heart defects by use of echocardiography or clinical database follow-up—24 critical and 29 serious defects (table 2). Additionally, 20 babies had significant congenital heart defects, but for the purpose of our main analysis were classified as six false positives and 14 true negatives.

Table 3 and figure 3G show that 26 (13%) of 195 newborn babies with an abnormal result with pulse oximetry had major congenital heart defects (18 critical cases and eight serious), and table 3 shows the sensitivity of pulse oximetry for critical cases and all major cases in the full cohort. Six critical and 21 serious cases were not identified by use of pulse oximetry (false negatives).

After retrospective review of all cases of identified congenital heart defects, 12 (50%) of 24 newborn babies with critical congenital heart defects had already been suspected at antenatal screening (figure 3A; table 4), whereas 19 (36%) of 53 major (critical and serious) cases were detected (table 4). 16 of 20,002 babies without critical or serious congenital heart defects were incorrectly identified at antenatal screening (figure 3A; table 4),

	Lesion	Timing of test (h)	Antenatal diagnosis	PO1 hand	PO1 foot	Examination result	PO2 hand	PO2 foot	Congenital heart defects category	Result
1	Transposition of the great arteries	3–6	Yes	81%	85%	Abnormal	Critical	True positive
2	Total anomalous pulmonary venous drainage	12–24	No	73%	77%	Abnormal	Critical	True positive
3	Aortic coarctation, hypoplastic aortic arch, ventricular septal defect	0–3	Yes	98%	72%	Abnormal	Critical	True positive
4	Pulmonary atresia, atrioventricular septal defect, transposition of the great arteries	3–6	Yes	83%	79%	Normal	84%	74%	Critical	True positive
5	Hypoplastic left heart syndrome	0–3	Yes	100%	96%	Abnormal	Critical	True positive
6	Transposition of the great arteries	3–6	No	53%	56%	Abnormal	Critical	True positive
7	Hypoplastic left heart syndrome	0–3	Yes	88%	86%	Normal	90%	90%	Critical	True positive
8	Aortic coarctation	12–24	No	95%	84%	Abnormal	Critical	True positive
9	Pulmonary atresia, double inlet left ventricle	0–3	Yes	93%	94%	Normal	93%	84%	Critical	True positive
10	Hypoplastic left heart syndrome	0–3	Yes	92%	97%	Normal	100%	97%	Critical	True positive
11	Hypoplastic left heart syndrome	0–3	Yes	91%	84%	Abnormal	Critical	True positive
12	Hypoplastic left heart syndrome	0–3	Yes	94%	94%	Abnormal	Critical	True positive
13	Transposition of the great arteries	3–6	No	79%	73%	Normal	69%	79%	Critical	True positive
14	Transposition of the great arteries, ventricular septal defect	3–6	Yes	83%	91%	Abnormal	Critical	True positive
15	Transposition of the great arteries	>24	No	96%	91%	Abnormal	Critical	True positive
16	Transposition of the great arteries	6–12	No	83%	74%	Abnormal	Critical	True positive
17	Pulmonary atresia, ventricular septal defect	0–3	Yes	79%	86%	Abnormal	Critical	True positive
18	Aortic coarctation	6–12	No	100%	96%	Abnormal	Critical	True positive
19	Aortic coarctation, hypoplastic aortic arch, ventricular septal defect	3–6	No	98%	97%	Abnormal	Critical	False negative
20	Congenitally corrected transposition of the great arteries, pulmonary stenosis	0–3	Yes	95%	97%	Abnormal	Critical	False negative
21	Transposition of the great arteries, ventricular septal defect, aortic coarctation	3–6	No	95%	97%	Normal	Critical	False negative
22	Hypoplastic arch, aortic stenosis, ventricular septal defect	>24	No	99%	99%	Abnormal	Critical	False negative
23	Tricuspid atresia, aortic stenosis	12–24	No	98%	96%	Abnormal	Critical	False negative
24	Hypoplastic aortic atresia, aortic coarctation, ventricular septal defect	12–24	No	98%	99%	Normal	Critical	False negative
25	Complete atrioventricular septal defect	3–6	Yes	92%	81%	Normal	93%	77%	Serious	True positive
26	Tricuspid atresia, atrioventricular septal defect	12–24	Yes	84%	84%	Abnormal	Serious	True positive
27	Tricuspid atresia, ventricular septal defect	0–3	Yes	87%	90%	Abnormal	Serious	True positive
28	Tetralogy of Fallot	3–6	Yes	87%	92%	Abnormal	Serious	True positive
29	Tricuspid atresia	6–12	No	93%	97%	Normal	94%	97%	Serious	True positive
30	Coronary artery fistula	12–24	No	88%	91%	Abnormal	Serious	True positive
31	Double outlet right ventricle, ventricular septal defect	0–3	Yes	93%	94%	Normal	88%	90%	Serious	True positive
32	Tetralogy of Fallot	0–3	Yes	93%	94%	Abnormal	Serious	True positive
33	Hypoplastic aortic arch, patent ductus arteriosus	>24	No	97%	92%	Normal	99%	97%	Serious	False negative
34	Anomalous left coronary artery	12–24	No	100%	100%	Normal	Serious	False negative
35	Ventricular septal defect	>24	No	98%	97%	Normal	Serious	False negative
36	Patent ductus arteriosus	>24	No	99%	100%	Normal	Serious	False negative
37	Aortopulmonary window	12–24	No	98%	100%	Normal	Serious	False negative
38	Pulmonary stenosis	3–6	No	97%	98%	Normal	Serious	False negative
39	Ventricular septal defect	>24	No	100%	100%	Normal	Serious	False negative
40	Pulmonary stenosis	>24	No	97%	96%	Abnormal	Serious	False negative
41	Atrioventricular septal defect	>24	No	97%	95%	Normal	Serious	False negative
42	Aortic coarctation, ventricular septal defect	>24	No	98%	100%	Normal	Serious	False negative
43	Ventricular septal defect	3–6	No	99%	97%	Normal	Serious	False negative
44	Aortic coarctation, hypoplastic aortic arch, ventricular septal defect	>24	No	100%	100%	Normal	Serious	False negative
45	Ventricular septal defect	6–12	No	96%	97%	Normal	Serious	False negative
46	Pulmonary stenosis	6–12	No	97%	98%	Normal	Serious	False negative
47	Pulmonary stenosis, ventricular septal defect	12–24	No	100%	100%	Normal	Serious	False negative
48	Pulmonary stenosis	12–24	No	99%	98%	Normal	Serious	False negative

(Continues on next page)

Lesion	Timing of test (h)	Antenatal diagnosis	PO1 hand	PO1 foot	Examination result	PO2 hand	PO2 foot	Congenital heart defects category	Result	
(Continued from previous page)										
49	Ventricular septal defect, atrial septal defect	>24	No	97%	98%	Normal	Serious	False negative
50	Ventricular septal defect	12–24	No	97%	99%	Normal	Serious	False negative
51	Tetralogy of Fallot	12–24	No	98%	99%	Normal	Serious	False negative
52	Ventricular septal defect	3–6	No	100%	100%	Normal	Serious	False negative
53	Tetralogy of Fallot	>24	No	99%	100%	Normal	Serious	False negative

PO1=first pulse oximetry test. PO2=second pulse oximetry test.

Table 2: Clinical details of babies with major congenital heart defects

	Critical cases alone	All major cases
True positives	18	26
False negatives	6	27
True positives	177	169
True negatives	19 854	19 833
Sensitivity	75.00% (53.29–90.23)	49.06% (35.06–63.16)
Specificity	99.12% (98.98–99.24)	99.16% (99.02–99.28)
Positive predictive value	9.23% (5.56–14.20)	13.33% (8.90–18.92)
Negative predictive value	99.97% (99.93–99.99)	99.86% (99.80–99.91)

Data are number or percentage (95% CIs).

Table 3: Accuracy of pulse oximetry in full cohort (n=20 055)

although this number was reduced to five cases after fetal echocardiography (figure 3B). One serious case was incorrectly diagnosed as having no congenital heart defects after fetal echocardiography (figure 3B).

For the cohort in which congenital heart defects were not suspected antenatally and therefore the results of pulse oximetry could affect postnatal management, pulse oximetry showed a higher sensitivity in critical cases (12 babies) than in major cases (35 babies; figure 3F; table 5). One (0.8%) in 119 babies without serious or critical congenital heart defects had a false-positive result with pulse oximetry (specificity 99.16%, 95% CI 99.02–99.28); this rate was similar for the full cohort and babies in whom congenital heart defects were not suspected antenatally (table 5).

169 babies in the full cohort who tested positive did not have major congenital heart defects. Six of these babies had significant congenital heart defects and a further 40 had respiratory or infective disorders that required medical intervention (antibiotics, oxygen therapy, or respiratory support). Thus, the total number of test-positive infants in whom there was neither significant congenital heart defects nor intercurrent illness who required treatment was 123 (63%) of 195 who were test positive or 0.6% of the total cohort.

Six newborn babies from the full cohort with critical congenital heart defects were falsely negative with pulse oximetry (table 2). One baby of six had suspected congenital heart defects after antenatal anomaly

screening, and in a further three babies the defects were identified before discharge from hospital because of an abnormal routine examination. Two babies were discharged home after both the pulse oximetry and postnatal examination were normal. Both babies presented with clinical symptoms relating to congenital heart defects and one (hypoplastic aortic arch and coarctation) presented in a collapsed state. Both went on to have cardiac surgery. No baby died with undiagnosed congenital heart defects in our study cohort.

A further 21 babies with normal pulse oximetry results were diagnosed with serious congenital heart defects. One of these had an abnormal clinical examination before discharge (pulmonary stenosis); the remaining 20 were identified through the use of the relevant databases. Three of these babies had aortic arch obstruction; however, most had non-life-threatening acyanotic disorders (table 2).

Median age at testing was 12.4 h for the full cohort. For the full cohort, earlier testing showed a strong association with increased sensitivity (odds ratio of true positives to false negatives with hours to testing as the explanatory variable was 0.93, 95% CI 0.88–0.98; p=0.0076), but this association became non-significant (0.97, 0.93–1.02; p=0.1953) when babies with antenatally suspected congenital heart defects were excluded (table 6). Rate of false-positive outcomes increased during earlier timings (odds ratio of false positives to true negatives, 0.99, 0.98–1.00; p=0.0217). This result did not change when babies who were suspected to have congenital heart defects antenatally were excluded (0.99, 0.98–1.00; p=0.0237).

Discussion

In asymptomatic infants, pulse oximetry had a sensitivity of 75% for critical lesions and 49% for all major lesions. Sensitivity was 58% for critical cases and 29% for all major cases in the cohort in which the test results could affect postnatal management because congenital heart defects had not been suspected antenatally.

False-positive results arose in 0.8% of newborn babies; however, 27% of the cohort with false-positive results had



Figure 3: Results of antenatal testing and pulse oximetry

(A) All recruited newborn babies. (B) 35 newborn babies were identified with antenatal screening for anomalies to have suspicion or high likelihood of congenital heart defects (all were based on anomaly scans). No cases of Down's syndrome were antenatally diagnosed. (C) Congenital heart defects in 23 of 35 babies, in whom echocardiography would be undertaken after birth irrespective of the results obtained with pulse oximetry, were confirmed by use of fetal echocardiography. (D) 12 newborn babies without congenital heart defects according to the results of fetal echocardiography. (E) 20 020 babies without suspicion of congenital heart defects by use of antenatal screening. (F) 20 032 babies in whom a positive result with pulse oximetry could make a difference to subsequent testing (most likely with echocardiography) and contingent health care. (G) In settings without antenatal testing, the whole cohort would benefit from the use of pulse oximetry. In settings with antenatal testing, but without fetal echocardiography, those in (E) are the appropriate group to undergo pulse oximetry. Two (one with serious congenital heart defects, the other without congenital heart defects) of 20 055 babies had missing fetal echocardiography results; we have made the assumption that these babies would undergo echocardiography after birth.

additional problems that required medical intervention (specifically significant congenital heart defects, respiratory disorders, and infections).

If the results from this study were applied to a population of 100 000 babies, roughly 264 babies would have major congenital heart defects. Of these, 130 would be identified by use of pulse oximetry. About 120 babies would have critical lesions and 90 of these would be detected by use of pulse oximetry. If an antenatal detection of 50% (that we noted in our study; figure 3A; table 4) is assumed, pulse oximetry could detect an additional 35 cases of critical congenital heart defects. This number is likely to be higher in areas with lower rates of detection with antenatal

	Critical cases alone	All major cases
True positives	12	19
False negatives	12	34
False positives	23	16
True negatives	20 008	19 986
Sensitivity	50.00% (29.12–70.88)	35.85% (23.14–50.20)
Specificity	99.89% (99.83–99.93)	99.92% (99.87–99.95)
Positive predictive value	34.29% (19.13–52.21)	54.29% (36.65–71.17)
Negative predictive value	99.94% (99.90–99.97)	99.83% (99.76–99.88)

Data are number or percentage (95% CIs).

Table 4: Accuracy of antenatal ultrasound scan (n=20 055)

	Critical cases alone	All major cases
True positives	7	10
False negatives	5	25
False positives	170	167
True negatives	19 850	19 830
Sensitivity	58.33% (27.67-84.83)	28.57% (14.64-46.30)
Specificity	99.15% (99.01-99.27)	99.16% (99.03-99.29)
Positive predictive value	3.95% (1.60-7.98)	5.65% (2.74-10.14)
Negative predictive value	99.97% (99.94-99.99)	99.87% (99.81-99.92)

Data are number or percentage (95% CIs).

Table 5: Accuracy of pulse oximetry in cohort in which a positive test would affect subsequent management (n=20 032)

ultrasonography. Furthermore, pulse oximetry is also likely to detect 30 cases of significant congenital heart defects and 199 cases of respiratory or infective illness that will require medical intervention. Of 100 000 babies, 843 would have an abnormal pulse oximetry but not have critical or serious congenital heart defects (false positives), but only 614 would be completely healthy (ie, no congenital heart defects or other illness). Early testing and the use of more conservative cutoff thresholds increase the rate of identification of babies with disease, but at the expense of slightly increased false-positive rates.

The validity of our findings depends on the quality of the study. The study population and recruitment criteria were well defined. Recruitment of consecutive eligible newborn babies was representative of a range of maternity activity. The sample size ensured that the study was of sufficient power to exclude clinically unacceptable accuracy. The index test was done by trained staff. The robustness of the reference standard was assured by echocardiography being

done by independent, trained individuals, and rigorous follow-up to 1 year of age for all recruited babies was undertaken to detect false-negative results.

This study is the largest UK test accuracy investigation of the use of pulse oximetry in the detection of congenital heart defects (panel 2). Most previous studies had few patients and were underpowered to address test accuracy.²⁶ Four cohort studies that were larger than ours have been reported.^{21-23,25} Sample size calculations were not reported in any of these studies. The prevalence of critical congenital heart defects after exclusion of most of the study population with congenital heart defects was low in three studies,^{21,22,25} which makes interpretation of the sensitivity especially difficult. Additionally, ascertainment of cases dying in the community or presenting elsewhere after discharge in these three studies was incomplete and might have resulted in inadequate accounting of false-negative results. Also in these studies, only postductal saturation measurements were used. If we had used a postductal saturation threshold of less than 95%, the number of false positives would have been reduced by 84, but three critical cases (two with hypoplastic left heart syndrome identified antenatally and one with coarctation of the aorta that was not diagnosed antenatally), one serious case (truncus arteriosus not suspected antenatally), two babies with significant congenital heart defects, and nine with respiratory disorders would also have been missed.

Granelli and colleagues²³ used preductal and postductal saturation measurements, but they used both preductal and postductal saturations of less than 95% and a difference of more than 3% as the test-positive threshold rather than only one measurement of less than 95% and the difference of more than 2% used in this study. Use of

	0-6 h	>6-12 h	>12-24 h	>24 h
Full cohort				
n=20 055	n=4956, 25%	n=4823, 24%	n=5323, 27%	n=4953, 25%
True positives	18	3	4	1
False negatives	7	1	8	11
False positives	60	40	38	31
True negatives	4871	4779	5273	4910
Sensitivity	72.00% (50.61-87.93)	75.00% (19.41-99.37)	33.33% (9.92-65.11)	8.33% (0.21-38.48)
Specificity	98.78% (98.44-99.07)	99.17% (98.87-99.41)	99.28% (99.02-99.49)	99.37% (99.11-99.57)
Cohort in which positive test would affect subsequent testing				
n=20 032	n=4937, 25%	n=4822, 24%	n=5320, 27%	n=4953, 25%
True positives	3	3	3	1
False negatives	6	1	7	11
False positives	59	40	37	31
True negatives	4869	4778	5273	4910
Sensitivity	33.33% (7.49-70.07)	75.00% (19.41-99.37)	30.00% (6.67-65.25)	8.33% (0.21-38.48)
Specificity	98.80% (98.46-99.09)	99.17% (98.87-99.41)	99.30% (99.04-99.51)	99.37% (99.11-99.57)

Data are number or percentage (95% CIs).

Table 6: Pulse oximetry with time of testing for detection of all major cases of congenital heart defects

Granelli and colleagues²³ threshold as an alternative in our study would have reduced the number of false positives by 61, but one critical case (hypoplastic left heart syndrome that was suspected antenatally), one serious case (truncus arteriosus), and one significant case (Ebstein's anomaly)—not suspected antenatally—and 13 cases of respiratory disorders would have been missed.

Granelli and colleagues²³ undertook full ascertainment of cases of congenital heart defects with a reference standard similar to that in our study. The prevalence of critical congenital heart defects in this study was almost identical to the prevalence we identified in our cohort. However, the antenatal detection rate of critical congenital heart defects was only 3%²³ compared with 50% in our cohort. Pulse oximetry was generally done much later in Granelli and colleagues' study²³ than in our study (median age 38 h vs 12.4 h); later testing and slightly less conservative testing thresholds were probably the main explanations for the lower false-positive rate of 0.17% reported in this study. However, the sensitivity for critical cases reported in our study was greater (75% vs 62%).²³

In all studies, some cases of critical congenital heart defects were not detected and, in keeping with our results, most critical cases that were missed were those with aortic arch obstruction. In our study, 43% of babies with critical coarctation or interrupted aortic arch were detected with pulse oximetry compared with 29% (four of 14) in Granelli and colleagues' study.²³

In our study, the reduction in the threshold for test-positive cases, inclusion of antenatally suspected cases, and a more even spread of timing of testing gives important insights into the optimum regimen for a potential screening programme. In view of the increasing trend towards early discharge and increased reporting of antenatally diagnosed congenital heart defects, our data are particularly important in this respect.

When combined with the routine anomaly scan and newborn physical examination screening, 92% of critical congenital heart defects were detected in our study cohort and no baby died with unidentified congenital heart defects. The detection rate of critical congenital heart defects with pulse oximetry was 75% in the full cohort, which is similar to that in other large studies.^{22,23} The detection rate for serious lesions is lower; however, most serious lesions that were not identified with screening were non-life-threatening acyanotic disorders (eg, ventricular septal defect, patent ductus arteriosus) that would not usually be associated with hypoxaemia. Therefore, early detection with low oxygen saturations is unlikely. The consequences of missing such lesions are important, but not as potentially devastating as missing the life-threatening critical lesions. The critical lesions most likely to be missed by use of pulse oximetry as a screening method were those causing obstruction to the aortic arch (eg, coarctation of the aorta and interrupted aortic arch) this is also a consistent finding in other studies.^{22,23}

Panel 2: Research in context

Systematic review

We searched Medline (1951–2011), Embase (1974–2011), and the Cochrane Library (2011) for systematic reviews and primary studies in which the accuracy of pulse oximetry was assessed for detection of critical congenital heart defects in newborn babies. Language restrictions were not applied. A combination of MeSH and text words was used to generate two subsets of citations, one indexing pulse oximetry ("pulse" NEAR "oximetry") and the other indexing outcomes ("infant-newborn", "neonate", "newborn", "infant", "congenital heart disease"). These subsets were combined with "AND" to generate a subset of citations relevant to our research question. We identified two systematic reviews^{26,28} and 12 primary studies.

Interpretation

The results of this study enhance the strong evidence that indicates potential benefits of predischarge screening with pulse oximetry as a routine procedure, and show the added value of such screening to current antenatal screening, and the timing and method of the procedure. Pulse oximetry has been identified as a safe, non-invasive, feasible, and reasonably accurate test, which has a sensitivity that is better than that of antenatal screening and clinical examination. It has been shown to add value to existing screening procedures and is likely to be useful in the identification of cases of critical congenital heart defects that would otherwise go undetected. The use of both preductal and postductal saturations seems to be advantageous compared with postductal saturation alone. Other advantages of pulse oximetry are that it can be used for detection of other defects such as significant congenital heart defects and respiratory and infective illnesses. The critical lesions most likely to be missed by use of pulse oximetry are those that cause obstruction of the aortic arch (eg, coarctation of the aorta and interrupted aortic arch).

Pulse oximetry is a safe, non-invasive, feasible, and reasonably accurate test, which has a sensitivity that is better than that of antenatal screening and clinical examination. The use of both preductal and postductal saturations compared with postductal saturation alone seems to be advantageous and in practice does not take much longer to do. It adds value to existing screening procedures and is likely to be useful for identification of cases of critical congenital heart defects that would otherwise go undetected. The detection of other diseases such as significant congenital heart defects, and respiratory and infective illnesses is an additional advantage. The results of this study enhance the strong evidence that indicates the potential benefits of the introduction of predischarge pulse oximetry screening as a routine procedure.

Contributors

AKE designed and managed the project. LJM contributed to the study design and did the statistical analysis for the test accuracy study. ATF was the trial coordinator, contributed to the study design, ensured that the protocol was implemented, and prepared data for analysis and reporting. AB undertook all the additional echocardiography, collated assessments of the echocardiograms, and provided cardiac liaison. JPD contributed to the study design, and supervised the study. ST contributed to the study design. JJD designed the test accuracy study, provided methodological input throughout, and oversaw the analyses and their interpretation. KSK designed the test accuracy study. All authors edited the report.

PulseOx Study Group

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This project was funded by the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 06/06/03) and will be published this year in full in *Health Technology Assessment*. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, National Health Service, or Department of Health. We thank the members of the joint steering and data monitoring committee for their assistance throughout the project—Gerben ter Riet (chair; Academisch Medisch Centrum, Universiteit van Amsterdam), Suzie Hutchinson (Little Hearts Matter), Carole Cummins (University of Birmingham), Sam Richmond (Sunderland Royal Hospital), and Stavros Petrou (University of Oxford). The PulseOx study was coordinated by Birmingham Clinical Trials Unit at the University of Birmingham and we acknowledge the work of all the staff involved in the study, especially Leanne Fulcher, who was the data manager, and Edward Tyler who designed and developed the study database. We thank John Wright and Tarak Desai (Birmingham Children's Hospital) for their advice with the assessments of echocardiograms and grading echocardiographic findings; all the echocardiographers who helped with the additional echocardiography required by the study, particularly Vishna Rasiah, David Roden, Mrinalini Rajimwale, and Askar Kukkadi; David Cunningham who searched the Central Cardiac Audit Database; and all the midwives and midwifery assistants who worked so hard with recruitment and screening and the women who consented to take part in the study.

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