Diplomarbeit

Epidemiology and risk factors of unfavorable course of congenital heart defects in newborns

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Affidavit

I certify on my honour that I have wrote the presented thesis independently and without the help of others, other than the specified sources were not used.
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Contents

Abbreviations

Ao or AO aorta; aortic

ASD atrial septal defect

BPD bronchopulmonary dysplasia

BPs sistolic blood pressure

CAVSD complete atrioventricular septal defect

CCTGA congenitally corrected transposition of the great arteries

CFI colour flow imaging

CFM colour flow mapping

CS coronary sinus

CHD congenital heart disease

CW continuous wave

HMD hyaline membrane disease

IDM infant of a diabetic mother

IMV intermittent mandatory ventilation

n\TN innominate artery MPA

IVC inferior vena cava MR

IVS interventricular septum MV

IVSD interventricular septum in NEC diastole

IVSS interventricular septum in PA systole PaCO2

L left

LA left atrium

LAVV left atrioventricular valve

LCC left common carotid artery

LPA left pulmonary artery

LV left ventricle

LVEED left ventricle end-diastolic diametr

LVEESD left ventricular end-systolic diametr

LVET left ventricular ejection time

LVIDd left ventricular internal diameter in diastole

LVIDs left ventricular internal diameter in systole

LVO left ventricular output

LVOT left ventricular outflow tract

LVPW left ventricular posterior wall

LVPWD left ventricular posterior wall thickness in diastole

LVPWESD left ventricular posterior wall end-systolic dimension

LVPWS left ventricular peak systolic wall stress

LVSV left ventricular stroke volume

M-mode movement mode

MPA main pulmonary artery

MR mitral regurgitation

MV mitral valve

NEC necrotizing enterocolitis

OF oval fossa

PA pulmonary artery

PaCO2 arterial partial pressure of carbon dioxide

PAIVS pulmonary atresia with intact ventricular septum

PAP pulmonary anerial pressure

MAP mean airway pressure

PDA patent ductus arteriosus

PFC persistent fetal circulation

PFO patent oval foramen

PML posterior mitral valve leaflet

PPAS peripheral pulmonary arteiy stenosis

PPHN persistent pulmonary hypertension of the newborn

prf pulse repetition frequency

PTC persistence of transitional circulation

PV pulmonary valve

Qp pulmonary blood flow

Qpda left-to-right ductal blood

Qs systemic blood flow

R right

RA right atrium

RAVV right atrioventricular valve

RPA right pulmonary artery

RV right ventricular

RVO right ventricular output

RVOT right ventricular outflow tract

SaO2 arterial oxygen saturation

SV stroke volume; single ventricle

SVC superior vena cava

ST supraventricular tachycardia

TAPVC total anomalous pulmonary venous connection

TGA transposition of the great arteries

ToF tetralogy of Fallot

TR tricuspid valve

VLBW very low birth weight

VSD ventricular septal defect

Predictors of unfavorable course of congenital heart disease in newborns

Introduction. Congenital heart defects (CHD) remain the most frequent of all congenital anomalies. Due to their high prevalence and mortality rate CHD is considered as an important public health issue all over the world: up to 22% of infants die in the first week of life, and 30-80% - in the first year of life. If CHD is early diagnosed, half of these children can be saved with the help of timely surgical intervention.

Materials and methods. Annual statistical reports were analyzed in details for the determination of morbidity and mortality rates among the infants suffering from the CHD in Odessa region for the period of 2007-2011. A retrospective analysis of 81 newborn case histories with CHD (1^{st} group) and 100 newborns without CHD (2^{nd} group) was performed. To identify the unfavorable course predictors, the 1^{st} group was divided into 2 subgroups: 1.1 - unfavorable course (death or an indication for immediate cardiac surgery), 1.2 - favorable course (presence or absence of clinical signs, but no indications for urgent cardiac surgery) . Statistical analyses were performed using STATISTICA 5, on-line calculator SISA CLARA.

Results. During the last 5 years, in the Odessa region CHD alone accounts for almost about 9% of neonatal morbidity and occupies the second place amidst the overall Congenital Anomalies. Isolated CHD is responsible for 7-8% of all neonatal mortality. The absolute mortality rate from CHD in last 5 years decreased from 0,56 ‰ to 0,45 ‰; proportional mortality rate is 67%. Statistically significant risk factors for CHD were diagnosed:TORCH-infection (OR = 2.83, 95% CI 4.1 - 16.1), the CHD in the mother (OR = 5.9, 95% CI 0.6 - 47, 03), and with a Bad Obstetric History (BOH) (OR = 1.4, 95% CI 0.4 - 2.5). Unfavorable course predictors of CHD during the neonatal period were prematurity, ARI in the first trimester of pregnancy, the presence of comorbid conditions, hypoxic-ischemic encephalopathy.

Conclusion. Optimization of early diagnosis and management of CHD could play a significant role in the reduction of neonatal mortality rate. Proper identification of the risk factors of CHD is a definite indication for performing an early neonatal screening: pulse oxymetry and echocardiography (if available) before the discharge of the child from the the health care facility.Unfavorable course predictors can also help to determine the optimal treatment measures of CHD during the neonatal

period.

Key words: congenital heart defects, predictors, newborns

Prädiktoren der ungünstigen Verlauf der angeborenen Herzfehler bei Neugeborenen

Einführung. Angeborene Herzkrankheit (AHK) ist weiterhin die häufigste aller angeborenen Anomalien.
Aufgrund Ihrer hohen Prävalenz und Mortalität AHK gilt als ein wichtiges Thema für die Public Health in der ganzen Welt: bis zu 22% der Säuglinge sterben in den ersten Wochen des Lebens, und 30-80% - im ersten Jahr des Lebens. Wenn eine KHK ist früh diagnostiziert, die Hälfte dieser Kinder mit Hilfe der rechtzeitigen chirurgischen intervention gerettet werden können.

Materialien und Methoden. Die jährlichen statistischen Berichte wurden analysiert, in der details für die Bestimmung der Morbidität und der Sterblichkeit unter den Säuglingen leiden der AHK in der region Odessa für den Zeitraum von 2007-2011. Eine Retrospektive Analyse von 81 Neugeborenen Krankengeschichten mit AHK (Gruppe 1) und von 100 Neugeborenen ohne KHK (2. Gruppe) durchgeführt wurde. Zur Identifizierung der ungünstigen Kurs Prädiktoren, die 1. Gruppe war unterteilt in 2 Untergruppen: 1.1 - ungünstige Verlauf (Tod oder eine Indikation für die sofortige Herz-und Gefäßchirurgie), 1.2 - günstig-Kurs (Anwesenheit oder Abwesenheit von klinischen Anzeichen, aber keine Indikationen für dringende Herz-Operation). Statistische Analysen wurden durchgeführt mit STATISTICA 5, on-line-Rechner SISA CLARA.

Ergebnisse. Während der letzten 5 Jahre, in der Odessa Region AHK allein entfallen fast 9% der neonatalen Morbidität und belegt den zweiten Platz, inmitten der Allgemeinen Angeborenen Anomalien. Isoliert AHK ist für 7-8% aller neonatalen Mortalität verantwortlich. Die absolute Sterblichkeit von AHK in den letzten 5 Jahren sank von 0,56 ‰ zu 0,45 ‰; proportionale Mortalitätsrate 67%. Statistisch signifikante Risikofaktoren für eine AHK diagnostiziert wurden: TORCH-Infektion (OR = 2.83, 95% CI 4.1 - 16.1), der AHK bei der Mutter (OR = 5.9, 95% CI 0.6 - 47, 03), und mit einem Schlechten Geburtshilflichen Vorgeschichte (OR = 1.4, 95% CI 0.4 - 2.5). Ungünstigen Kurs Prädiktoren für AHK während der Neugeborenen waren auchFrühgeburten, ARI im ersten Trimester der Schwangerschaft, die Anwesenheit von Begleiterkrankungen, hypoxisch-ischämische Enzephalopathie.

Fazit. Optimierung von Früherkennung und management der AHK konnte spielen eine bedeutende Rolle bei der Senkung der Neugeborenen-Sterblichkeit. Richtige Identifizierung der Risikofaktoren der AHK ist eine eindeutige Indikation für die Durchführung einer frühen neonatalen screening: Puls oxymetry und Echokardiographie (falls vorhanden) vor der Entlassung des Kindes aus der

medizinischen Einrichtung. Ungünstigen Kurs Prädiktoren können auch helfen, um die optimale Behandlungsmaßnahmen der AHK während der neonatalen Periode zu bestimmen.

Schlüsselwörter: angeborene Herzkrankheit, Prädiktoren, Neugeborene

1. Literature review

Background

Epidemiology, early diagnosis and optimization of the management of congenital heart defects detected in neonatal period

Congenital heart and great vessels defects are among the most frequent congenital anomalies, that could be detected by newborns. In childhood and in later adult life they are also a major cause of infant mortality and morbidity. A prevalence indicating by recent population-based epidemiological studies of CHD is ranging from 4.6 to 12.2 per 1000 live births [4,8], thougt it varies in dependance from case definition and method of its determination. Congenital heart defects (CHD) are requiring the high cost of medical treatment and are representing an important problem of public health. CHD occurs in the most patients as an isolated malformation, but about 32% have also associated anomalies.

According to epidemiological studies in the world and in Ukraine, the detection rate of CHD in children ranges from 4 to 10 cases per 1000 live births. In most countries the relatively high share of the CHD diagnosed prenatally is to be seen. There is still an indicator of late CHD postnatal diagnosis [3, 4, 9, 11,12].

The most deaths occurring in the first year of life and up to 3% of all infant mortality and 46% of all deaths from congenital malformations. Associated extracardiac anomalies incidence ranges from 6% to 43%. Approximately 1/4 of the children are having critical congenital heart defects (CCHD), which require catheter intervention or surgery in the first year of life. [1]

Origin of the samples (collected from all live births/all births), the source of information (birth/ death certificates) and paediatric cardiologist, that performs the examination – are the factors, that definite the incidence of congenital heart defects (CHD). Differences in methodologies, which are used in various studies are resulting in wide variation between prevalence and incidence in reports of associated malformations, as well in ethnic occurrence and regional differences. The spectrum of CHD is in the last 10 years stayed remarkably constant, due to the reports of recent investigations.

The inclusion of early spontaneous abortions in the data pool can make the incidence remarkably higher. Current incidence of CHD, reported in recent studies, ranges between 4.05 to 10.2/1000 live births.[2] Potential cause of lower earlier reported incidence of CHD of 3-5/1000 live births is an inadequate diagnostic procedures and ineffective surgical interventions [11]. With early diagnosis, half of these children could have a successful surgical treatment and their lives can be saved [2, 4].

The average number is almost certainly under-ascertained, because the registries are including data, based on diagnoses after the neonatal period, and also echography data reports, which show a prevalence of 8-10 per 1,000 [22]. Severe heart defects, e.g. 39% of transposition of great vessels, and 73% of hypoplastic left heart, are quite commonly prenatally diagnosed [EUROCAT, 2007]. The actual findings of live birth prevalence of congenital heart defects represents 6.1 per 1,000 births, which is the largest group of congenital anomalies. The reported increase of congenital heart defects prevalence is probably connected with increased trend to early echography of babies with a heart murmur.

Congenital heart defects (CHD) are defined as a structural heart or intrathoracic great vessels abnormalities which have actual or potential functional significance. CHD is a spectrum of conditions, some of which may be fatal in the neonatal period, and from some of them a normal lifetime duration could be expected. At 10-30% patients, dead from congenital heart defects, the condition was not diagnosed before autopsy.[3,17,22]

A duct dependent circulation is present in about 1-1.8 babies per 1000 live births, which demands a persistent ductus arteriosus (PDA) being necessary for survival. These patients are representing a particular risk group, which is also supported by an increasing worldwide trend to the early discharge from maternity units, because the effects of ductal closure may not manifest during early discharge examination.

1.2 Classification of Congenital Heart Defects:

I. [Rahilly & Mὺller]

- *Cyanotic CHD (Right to Left Shunt)*
  - 5 Ts (D-TGA, TOF, Truncus Arteriosus, Tricuspid Atresia, TAPVR)
  - DORV (Double Outlet Right Ventricle)
  - ESP (Anomaly of Ebstein, Single Ventricle, Pulmonary Atresia/Critical Stenosis)
- *Systemic Hypoperfusion and Congestive Heart Disease (Cyanosis maybe mild initially)*
  - –Hypoplastic Left Heart Syndrome (HLHS),
  - –Aortic Stenosis, Coarctation of Aorta, Aortic Arch Interruption,
  - Cardiomyopathies etc.
- *Acyanosis with no or Mild Respiratory Distress*

– VSD, ASD, Endocardial Cushion Defect, PDA, Aorto-pulmonary Window, L-TGA, PAPVR.

II. [Artman, Mahony, Teitel]

- *Duct-dependent CHD (Left or Right Sided)*

[Transposition of Great Arteries, Syndrome of Hypoplastic Left or Right Heart, Total Anomalous Pulmonary Venous Return]

- *CHD with an enrichment of the pulmonary circulation with left to right shunt* [VSD, ASD, PDA]
- *CHD with the depletion of the pulmonary circulation*

[Pulmonary Stenosis, Tetralogy of Fallot]

- *CHD with unchanged pulmonary blood flow*

[Aortic Coarctation, Interrupted or Hypoplastic Aortic Arch]

- *CHD manifested with cardiac arrhythmias or as cardiomyopathies*

[Complete AV block, Paroxysmal Tachycardia, PFO with conduction disterbence etc.]

1.3 Risk factors for Congenital Heart Disease (CHD):

All the factors can be divided into factors of direct damage (teratogenic effects, physical and chemical environmental factors, infections, bad habits, medications) factors and indirect effect through utero-placental blood flow.

Great significance are having:

Antenatal detection:

Congenital heart defects of a child in pregnancies without risk factors are staying undetected up to delivery. Routine antenatal screening for CHD, which is a part of anomally screening, is performed at the gestational age of 20 weeks and mostly limited to a four-chamber view of the heart. This examination can reveal around 25% of significant CHD, which can be significantly improved due to specific training of performing physicians and assessment of the ventricular outflow tracts.

The role of fetal echocardiography is dedicated to 5% of pregnancies with the identified risk factors or detected abnormality due to routine antenatal scanning, but in the experienced hands, this method can become sensitive as well as specific.

Anamnesis:

On the influence of heredity on the formation of the CHD is evidenced by the fact that in the families where parents (especially mothers) have a CHD, the probability of this pathology in children is 3-5 %. In the presence of defects of the left half of the heart, this frequency increases to 10-15 %. A CHD at a sibling gives a 2% risk on a subsequent child.

Associated Syndromes:

Congenital heart diseases have complex and multifactorial aetiology. A list of recognised associations include:

- Single gene defects: Noonan's, Marfan's, isomerisms;
- Teratogens: anticonvulsants, alcohol, lithium;
- Congenital infection: rubella, cytomegalovirus
- Contiguous gene syndromes: William's, Di-George's;
- Chromosomal abnormalities: Down, Edward, Patau, Turner, Cri-du-chat;

Even the mechanisms determinating the association of Down syndrome with congenital heart defects are now first beginning to be studied.

1.4 Assessment of a child with suspected CHD:

During initial case assessment the following information has to be assembled:

- Antenatal: Routine anomaly and fetal echocardiography.
- Perinatal: Considering risk factors for infection and persistent pulmonary hypertension (PPHN) that may present in a way indistinguishable from CHD.
- Postnatal: Breathing and feeding difficulties.
- Risk factors: Family history, maternal medication or congenital infection.

An asymptomatic murmur can be detected on the routine neonatal examination in the neonatal period or when an infant becomes symptomatic. During the infant assessment with possible CHD, risk factors and anamnesis should be taken into consideration. The defects, especially with significant left ventricular tract obstruction are manifesting before the 2nd examination, which can be a cause of high mortality if they continue to go unrecognised.

A routine neontatal examination can reveal round 45% of congenital heart defects, but at the same time a big ammount of innocent murmurs can be also detected. However, at this period a wide

ductus arteriosus can disturb the early identification of severe abnormalities. [4] Current guidelines recommend initial screening for CHD in the neonatal period with a repeated examination in 6–8 weeks.

Currently, the Centre for Disease Control and Prevention (CDC), USA is working for identification of the causes and to prevent prevention of birth defects, including congenital heart defects. Applied public health approach incorporates three essential elements: prevention research and programs, appropriate studies for causes identifications, surveillance or disease tracking [7].

1.5 Surveillance of Congenital Heart Defects :

CDC has established population based birth defects surveillance systems to be able to manage congenital heart defects. These systems are used as a basis for research studies, developed to identify potential causes and opportunities for congenital heart defects prevention. Information obtained from these systems is used to understand identify health predisposal factors in the occurrence of CHD, survival of children, special features of patients, plan for outcome and life expectancy improvement, help to ensure that children with CHD receive necessary medical care and services, as well as information from surveillance systems.

Preventable Causes Identification:

The formation of CHD is multifactorial. Identifying risk factors is an important aspect of prenatal and early postnatal diagnosis of CHD.

Population-based - National Birth Defects Prevention Study - is designed to evaluate the occurrence of disease in a large group of probands. All the factors can be divided into factors of direct damage (teratogenic effects physical and chemical environmental factors, infections, bad habits, medications) factors and indirect effect through utero-placental blood flow. Collapse prior to diagnosis and treatment and clinical deterioration are the major contributors that increased infant morbidity and mortality.

All the factors can be divided into factors of direct damage (teratogenic effects physical and chemical environmental factors, infections, bad habits, medications) factors and indirect effect through utero-placental blood flow. Identifying risk factors is an important aspect of prenatal and early postnatal diagnosis of CHD. It is known that at 70-80 % of children whose mothers suffered rubella in the first trimester of pregnancy, have the CHD [5]. The frequency of CHD almost 3 times higher in newborns of mothers suffering from alcoholism. Diabetes with poor glycemic control is a proven risk factor for transposition of the great vessels, coarctation of the aorta, hypoplasia of the

left ventricle. Risk factors of defects is the mother's age of 15-17 years and older than 40 years. In premature infants CHD meet 2 times more often.

That is an important factor to ensure the study results applicability to a definite population. Some important aspects about definite exposures during pregnancy, that can increase the risk of congenital heart defects development, were reported in recent CDC studies, like:

1. Smoking during the month before pregnancy till the end of the first trimester were more likely associated with congenital heart defect in a child.

2. Women with diabetes diagnosed before pregnancy are more at risk of having a child with a various birth defects, including congenital heart defects.

3. Women who were obese before pregnancy are having an increased risk of pregnancy accompanying by a congenital heart defect.

High proportion of infants with severe heart defects are diagnosed for the first time after discharge from hospital after birth. The general prenatal detection rate of CHD remains low even in European countries. Data, which were obtained on maternal age, associated risk factors, time of diagnosis, type of CHD and outcome [10] showed that a high mortality was associated with the presence of extracardiac anomalies in 71 (32%) and prenatal cardiac failure in 28 (13%).

Prenatal diagnosis, as well as early detection of the cardiac anomaly are playing an important role in improving the prognosis of patients and management strategies for neonatal CHD. Clinical deterioration can be reduced by appropriate early management due to early detection of congenital heart disease in the asymptomatic period immediately after birth.[7]

The outcome for congenital heart disease, which were diagnosed in utero is low. Although increase in the number of cases, that were detected prenatally, is explained by progressive increase in the number of cases referred for fetal echocardiography. Patients, who were involved in the management and were counselled again after diagnosis of heart defect in early pregnancy must be checked on the presence of the additional risk factors, that can influence prognosis. These factors can also be used as predictions structural cardiac defects outcome, which were prenatally detected by fetal ehocardiography [9].

A detailed study from Northern Norway was reviewing the data of all perinatal autopsies performed during the study period and all fetal and neonatal echocardiographies to evaluate shortcomings of severe congenital heart defects pre- and postnatal diagnosis [11]. Although prenatal ultrasound screening is universal and at least one neonatal examination is usually made before discharge, the diagnosis of major CHD is often made after a relevant delay.[8] Earlier recognition of treatable abnormalities may improve the perinatal outcome. Moreover, some forms of heart disease progress in severity during fetal life.

In significant proportion of cases the diagnosis of major CHD is made after a relevant delay, though performing of universal prenatal ultrasound screening and at least one neonatal examination before discharge. The high rate of pregnancy termination after the detection of a severe cardiac defects is considered to be one of the main reasons for this is.

A heart murmur or other cardiovascular abnormalitie identified in an asymptomatic infant, as well as the development of symptoms and signs that could be attributable to CHD, have to be considered as two main reasons for a diagnosis of CHD in the neonatal period. Early detection of ductal-dependent cardiac malformations prior to ductal closure is, however, of significant clinical importance, as the treatment outcome is related to the time of diagnosis. Approximately half of all newborns with congenital heart defects are asymptomatic in the first few days of life.

Pulse oximetry has been proposed as the method of early detection for congenital heart diseases. Among the main aims of the screening were:

1) The determination of the pulse-oximetric screening effectiveness, which was performed on the first day of life in healthy newborns for the detection of congenital heart disease;

2) The determination if a pulse-oximetric screening combined with clinical examination is more exact in the diagnosis of congenital heart disease in comparison to clinical examination alone.

Heart murmurs, tachypnea and cyanosis are the basic physical examination findings, that help to suspect a CHD in neonates. The diagnosis of CHD is established by a variety of examination methods. These symptoms are not always manifested before the discharge from hospital.

Currently infants are screened for the detection of congenital heart defects after birth during initial physical examination, next examination is performed at six to eight weeks after birth. However, this method of screening fails to detect up to 50% of congenital heart defects at birth.[6] According to a recent study from the United Kingdom, up 25% of infants with CHD were not diagnosed until discharge, meanwhile median age of diagnosis was 6 weeks. [13] Early detection of congenital heart defects in the asymptomatic period immediately after birth will reduce clinical deterioration by instigation and appropriate interventions.

1.6 Detailed Assessment of a Neonate with suspected CHD:

The following information needs to be obtained at the initial review:

Risk factors: Family history, maternal medication or congenital infections.

Antenatal factors: Routine anomaly and fetal echocardiography.

Perinatal factors: Risk factors for infection and persistent pulmonary hypertension.

Postnatal factors: Breathing and feeding difficulties. Excess weight gain or failure to lose weight after birth.

Clinical examination :

A full examination should include: evaluation of airway, breathing and circulation; **a**ssessment and management of life-threatening problems. Presence of dysmorphic features and other congenital abnormalities. Colour: Cyanosed or pale. Check oxygen saturation with a pulse oximeter. Signs of respiratory distress: respiratory rate, recession and grunting.

Heart rate. Palpation of pulses: Discrepancy between right and left brachial pulses with weak femorals suggest the possibility of an aortic arch abnormality.

Presence of thrills: In the upper sternal edge and suprasternal notch will suggest severe or critical pulmonary or aortic stenosis that may be ductdependent. Auscultation for murmur: Timing, site and radiation. Palpation for hepatomegaly: A large liver indicates heart failure or elevated right heart pressures. Auscultation for bruit: For cerebral or hepatic arterio-venous malformations.[4]

1.7 Clinical Significance of Pulse oximetry Screening :

The method of pulse oximetry has gained wide acceptance as noninvasive in determinations of oxygen saturation (SaO2). Among the advantages of this method: it is able to provide instantaneous data, does not require calibration and correlate well with blood gas measurements. The median value at 20 to 24 hours of life (97.8%) is similar to the results for healthy full-term infants between 2 and 7 days of age (97.6%). The question that has to be studied, given this association, is whether oximetry can successfully help to diagnose CHD in newborn population, suspected to have heart defect. [1]

O'Brien and colleagues have defined reference data for oxygen saturation in healthy fullterm infants during their first 24 hours of life. Hoke and colleagues, using a cutoff of 95% in lower-extremity saturation, suggested that could be identified 81% of neonates with CHD. [14]

For the typical newborn with a hemoglobin concentration of 20 g/dL, cyanosis will only be visible when arterial oxygen saturation is < 80%; if the infant only has a hemoglobin concentration of 10 g/dL, the saturation must be < 60% before cyanosis is apparent. Generally, to produce visible central cyanosis 4 to 5 g of deoxygenated hemoglobin is needed, independent of hemoglobin concentration.

Pulse oximetry provides estimation of arterial oxyhemoglobin saturation (SaO2) by utilizing selected wavelengths of light to determine the saturation of oxyhemoglobin noninvasively (SpO2). Hypoxemia, which is a common sign of many forms of CHD, comes from the mixing of systemic and venous circulations. Hypoxemia can also result in obvious cyanosis. Importantly, those children with mild hypoxemia, with arterial oxygen saturation of 80% to 95%, will not have visible cyanosis.

Different oximeters, measuring either functional or fractional saturation, various probe sites and different cut-off values for saturation were the reasons for an unsuccessful attempt to evalutate the method sensitivity, basing on a meta-analysis. Non-invasive measurement of oxygen saturation has been proposed as a screening method for early detection of duct dependent defects.[1,3]

Great efforts have been made to screen duct-dependent congenital heart defects in the newborn. Arterial pulse oximetry screening (foot and/or right hand) has been put forth as the most useful strategy to prevent circulatory collapse. The impact of pulse oximetry screening on the detection of duct dependent congenital heart defects was investigated in a Swedish prospective screening study with the involvement of 39821 newborns, as well as to formulate the strategies to maximise sensitivity while minimising false positives in a screening test for duct dependent circulation with a new generation oximeter which measured functional oxygen saturation preductally [in right hand] and postductally [in either foot]. The left hand, until then, has always been ignored, because it was unclear if the ductus arteriosus influences left-hand arterial perfusion. Also has been reached at optimal screening cut-off values of <95% saturation or >3% difference between right hand and foot. [18]

Pulse oximetry screening of asymptomatic newborns has been suggested as a life-saving procedure for the early detection of critical congenital heart disease (CHD) in asymptomatic newborns. An elective state-directed public health screening program was evaluated in Middle Tennessee using a saturation value of 94% defined as *'normal'*. This study demonstrated problems with the screening and found the positive predictive value was less than 1% and also conclued that before universal screening can be implemented.[Journal of Perinatology 31, 125-129 (Febr 2011)].

As it was concluded in a prominent Swiss study, arterial oxygen saturation on both hands and on one foot was measured within the first 4 hours of life with the exception of some neonates with complex or duct dependent congenital heart defects and some children with persistent pulmonary hypertension. The type of oximeter used to have a significant effect on both the detection rate and false positive rate.

1.8 Limitations and Challenges to Neonatal Pulseoximetry in Detection of CCHD:

Technical differences between the various types of oximeters in general use include measurement of functional or fractional oxygen saturation, preset signal-averaging times, and methods for the exclusion of motion artifact. The following technical limitations have to be considered to perform oximetry measurement in the newborn. When continuous pulse oximetry is

used, the mean SpO2 in the newborn at 24 hours of age is 97% to 98%, however, multiple investigators have demonstrated periodic and sustained desaturation below 95% during sleep, feeding & crying.[1]

Oximetry screening before 24 hours of life can result in a significant number of false-positive results. It must be always taken into consideration that motion artefacts, low peripheral perfusion, partial probe detachment, probe placement, dyshemoglobinemias and hyperbilirubinemia can be associated with falsely low oximetry readings in the newborn population.

A recent update from Hong Kong revealed that the pulseoximetry also have a number of limitations which may lead to inaccurate readings. Moreover, a study from the United Kingdom reported that the false-positive rate was as high as 5% when oximetry screening was performed in the first 24 hours compared with 1% at the time of hospital discharge. [9] Arterial oxygen saturation varies considerably in the first 24 hours, with many healthy newborns having arterial saturations of less than 95%. Ideally oximetrie should be used soon after delivery, because newborns with CCHD are usually having clinical deterioration in the first 48 hours of life.

Potential causes of inapropptiate pulseoximetry parameters:

1. Methylene blue, indocyanine green and indigocarmine, used intravenous, can cause falsely low SpO2 parameters.

2. Falsely reassuring pulse oximetry reading in case of CO poisoning may mask life-threatening arterial desaturation. When dysfunctional hemoglobin is suspected to be present, co-oximetry is required to accurately measure the oxyhemoglobin level. Pulseoximeters use two-wavelength spectrophotometry (660 nm and 940 nm), that is why the presence of dysfunctional hemoglobins such as carboxyhemoglobin and methemoglobin can cause inaccuracies. External interference:

3. Pulse oximetry readings may be affected by profoundly decreased hemoglobin concentration (Hb<5g/dL).

4. A reduction in peripheral pulsatile blood flow produced by peripheral vasoconstriction (severe hypotension, cold, hypovolemia, cardiac failure) or peripheral vascular disease.

5. Several studies have found that the accuracy and performance of pulse oximeters are affected by deeply pigmented skin, but data on the effect of skin pigmentation on pulse oximetry readings are conflicting.

6. Because of the sigmoid shape of oxygen-haemoglobin dissociation curve oximetry is relatively insensitive in detecting the development of hypoxemia in patients having high baseline levels of PaO_2.

7. Inability to detect saturation below 80% with the same degree of accuracy and precisionseen at higher saturation.

8. Tricuspid regurgitation manifesting with venous congestion, may produce venous pulsation which may result low readings with ear probes as venous oxygen saturation is recorded by the oximeter.

1.9 Optimization of Medical Management of CHD in the Neonatal Period:

Management of a neonate with suspected duct-dependent CHD implies overall improvement of the general condition i.e.

- Airway, breathing and circulation. May consider early endotracheal intubation and ventilation.
- Correction of acidosis, hypoglycaemia, hypocalcaemia and other electrolyte abnormalities.
- Echocardiography, performed by a competent echocardiographer is available.
- Infusion of Prostaglandin E.
- Sepsis and metabolic diseases should be considered in the differential diagnosis and appropriately treated.
- Other aspects to management

The parents should be informed of their infant's progress throughout. Transfer to tertiary services for definitive diagnosis and essential management is necessary for all infants with CHD becoming symptomatic. Transfer of the infant should be carried out exceptionally by an expert team of intensivists. Early discussion with a tertiary paediatric cardiology facility will allow optimisation of appropriate management.

Echocardiography is not immediately available in most centres. That is why careful clinical assessment of vital signs is deciding whether a newborn baby could be reasonably and safe to discharge home. The most important aspects are careful evaluation and early diagnosis of CHD. A few babies will present in poor condition, despite screening procedures, when the duct closes and CHD becomes manifesting. When any baby becoming unwell in the first weeks of life, CHD should be suspected. These babies may have had no or minimal cardiovascular signs at the newborn examination. Echocardiography remains the gold standard for the description of specific lesions however most infants can be stabilised without this facility before transfer to paediatric cardiology facilities. [15]

1.10 Conclusions:

Pulse oximetry is an invaluable contemporary monitoring technology. However, to inappropriate management of the patient can lead the following causes: device limitations, false negative results for hypoxemia and/or false positive results for normoxemia or hyperoxemia. Ultimately, the clinician is the monitor. Routine pulse oximetry performed on asymptomatic newborns after 24 hours of life, but before hospital discharge, may detect CCHD.[1]

Routine pulse oximetry performed after the twenty four hours of life in the institutions that have on-site pediatric cardiovascular services incurs very low cost and risk of harm.

Future studies in larger populations and across a broad range of newborn delivery systems are needed to determine whether this practice should become standard of care in the routine assessment of the neonate. In an analysis of pooled studies of oximetry assessment performed by the The American Heart Association [AHA] and The American Academy of Pediatrics [AAP] after 24 hours of life, showed the estimated sensitivity for detecting CCHD was 69.6%, and the positive predictive value was 47.0%; however, sensitivity varied dramatically among studies from 0% to 100%. False-positive screens that required further evaluation occurred in only 0.035% of infants screened after 24 hours.

The main purpose of this literarure review is to address the state of evidence on the routine use of pulse oximetry in newborns to detect critical congenital heart defects [CCHD]. Currently, CCHD are not detected in some newborns until their hospital discharge, which results in significant morbidity and occasional mortality.

2.Material and Methods:

2.1.Subjects:

The aim of the study is to analyse the morbidity and mortality due to congenital heart defects (CHD) among the newborns (i.e. up to first 28 th day of postnatal life) in the Odessa region during the period of 2007-2010.

A retrospective cohort study was conducted to determine the spectrum of congenital heart defects during the neonatal period (n=60) along with detailed analysis of the same and follow up of the disease course & outcome (CHD) in the Odessa region.

The retrospective case control study was carried on to reveal the risk factors of CHD in the region.

The first group ($Group_1$) was consisted of the newborn babies (n=81) who were born with congenital heart disease and the second group ($Group_2$) reflected the control group* (n=100).

Control group was consisted of 100 newborn babies without CHD.

All survived newborn babies (through the neonatal period) according to the severity of the malformation, co-morbid condition and clinical manifestation belonging to $Group_1$ who were either discharged from the maternity hospital with further follow up advice & recommendation with subsequent echocardiographic evaluation or had been transferred to to tertiary centre for the advanced care.

Data were collected from specially designed research protocol which included detailed information of maternal obstetric history, condition of the child soon after birth and the dynamics of clinical courses in the early neonatal period in the light of semiotics and para clinical investigations.

This part of the study was carried out in the Division of Neonatal Intensive Care Unit (NICU) and Division of Cardiovascular Surgery of Odessa Regional Paediatric Clinical Hospital (OOPCH).

Screening based prospective study: Determination of the diagnostic value of pulse-oximetry (specificity and sensitivity) among the newborn babies in the Odessa region during the first two days of life (i.e. before the discharge of the neonates from the maternity hospitals) for the early diagnosis of congenital heart disease (n=371). Four (4) neonates were excluded from the study out of the total number of observed patients (i.e. 375) for having severe respiratory pathology (RDS) and/or with very critical condition.

Measurement of SaO_2 were done in the Division of Neonatal Intensive Care Unit (NICU), Step and also in the Postnatal Ward of the Odessa Oblast Perinatal Centre.

Retrospective case control cohort study was also proceeded to determine the Predictors of Unfavourable Outcomes (PUO) of congenital heart disease (CHD) during the neonatal period.

This study cohort was divided in to two groups.

$Group_1$ – neonates born with critical congenital heart disease (CCHD, where the n=20) and, $Group_2$ – neonates having non-critical congenital heart disease (N-CCHD, where n=40).

2.2 Study Procedure:

Every member of the study cohort were meticulously followed up according to a standardized research protocol with detailed clinical and laboratory findings.

Patients history (81 Neonatal Bed Head Ticket) were analyzed from the archive of the Odessa Oblast Paediatric Clinical Hospital for the retrospective case control cohort study.

For the prospective observational study (371 neonates who were born in the Odessa Oblast perinatal Centre) at the time of the first SaO_2 measurement (usually between the first twelve to forty-eight hours) the study protocol was duly filled up. Depending on the dynamics of the clinical course after the 48 th hour necessary additional informations were also updated and analyzed till the 28 th day of post natal life. Pulse oximetry was performed in a quiet alert state at the age of 12 to 48 hours (median 28 hours) to evaluate the diagnostic value of screening to find out the presence of CHD among those (n=371) newborns. SaO2 was measured in the right arm and leg. Investigations were carried out at a ambient room temperature (with an average of 26-30◦C) and without supplemental oxygen (FiO_2- 0.21) using the new generation apparatus (Massimo Set, Rad-87 Pulse Co-Oximeter – Horizontal,USA).

Children with SpO2 <95% in the arm or leg placed in a separate group, which required additional clinical and instrumental examination to identify or rule out CHD and accordingly all neonates were divided in the respective groups:

True positive (SpO2 <95%, CHD is present) false positive (SpO2 <95%, there is no CHD) false negative results (SpO2 ≥ 95%, CHD is present) true negative (SpO2 ≥ 95%, there is no CHD). Additionally, each case was evaluated where the difference between measured SpO2 in the extremities found out to be greater than 3% or more.

To determine the predictors of poor prognostic outcome amidst the all identified neonates who suffered from CHD, two following subgroups were created:

1.1 – neonates with an unfavorable consequence (died or developed heart failure, or had an indication for immediate cardiac surgical intervention) and

1.2 – neonates with a favourable consequence (clinical manifestations of CHD may be present or absent, but no sign of heart failure and/or babies without any indication for immediate cardiac surgery).

Study protocol was divided in to three main segments based on the questionnaire:

- *Introductory part* (which included the patient's 'passport' data, Clinical/Path-anatomical diagnosis, accompanying co morbid condition, Complications, Detailed of the neonatal course encompassing the DOB, TOB, Anthropometrical measurements, Feeding type, Maternal anamnesis, HIV status, Obstetrical/Gynaecological history & Clinical course of the present pregnancy and labour).

- *Evaluation part* (which included the details of the disease course divided in to four sequential subgroups (based on horal criterion) through out the early and late neonatal period i.e. 1-24 hours, 25-48 hours, 3-7 th days and 2-4 th week of post natal life and assessment records according to clinical and instrumental parameters).

- *Interventional part* (which included the details of therapeutic and/or surgical approach towards the CHD were conducted).

The patients with Congenital Heart Disease were divided in to three major groups:

- Asymptomatic CHD in the neonatal period.
- Symptomatic CHD but without heart failure in the neonatal period.
- Symptomatic CHD with heart failure in the neonatal period.

2.3 Instrumental findings:

1. Auscultation: evaluate tachycardia, to determine the presence of cardiac murmur (timing, site and radiation.). Bruits for cerebral or hepatic arterio-venous malformations.

2. Blood pressure (BP): monitoring of BP in all extremities for the detection of possible Critical Coarctation of Aorta (CCoA).

3. Pulseoximetry (SaO_2): measuring the pre and post ductal oxygen saturation in right hand and right foot.

4. Hyperoxia test: to exclude the manifestation of congenital heart disease from extra cardiac pathology.

5. Arterial Blood Gas Analysis (ABG): to assess the homeostatic compromises depending upon the critical/non critical congenital heart disease (CCHD/NCCHD).

6. Electrocardiography (ECG): to demonstrate axis and rhythm abnormalities.

7. Roentgenography (X-Ray): to exclude pulmonary and extra pulmonary pathology, assessment of cardio-thoracic index (CTI) to determine the cardiomegaly and specific signs related to congenital heart disease (CHD) viz. Boot Shaped Heart (Pulmonary Atresia, Tetralogy of Fallot, Tricuspid Atresia), Snowman appearance (Total Anomalous Pulmonary Venous Return), Egg Shaped Heart/Egg on a String (Transposition of Great Vessels).

2.4 Statistical Analysis:

Statistical analysis of the parameters were done with the help of the software STATISTICA 5 and on-line calculator SISA CLARA.

Risk factors and predictors of poor prognosis were evaluated according to the monofactorial analysis and with calculation of odds ratios (OR).

Diagnostic value of newborn screening with pulse oximetry was evaluated by calculating the number of statistical indicators: diagnostic sensitivity (DSen), the diagnostic specificity (DSpe), positive predictive value (PPV/VP+), negative predictive value (NPV/VP-) the likelihood ratio for a positive result (LR+), the likelihood ratio for a negative result (LR-).

According to the recommendations of the WHO working group of experts to develop the principles of evidence-based medicine, diagnostic criteria (tests) affect the Post-test Probability of Disease (PPD), which manifests itself as follows: LR+ value above 10, and VP- below 0.1 - a significant impact; VP+ 5-10, and 0 VP- ,1-0, 2 - moderate impact; VP+ 2-5, and 0.2-0.5 VP- negligible impact; VP+ 1-2 and 0.5-1 VP- no effect.

All indicators were calculated 95% confidence interval (95% CI).

Significance of differences between other parameters were determined by methods of variational statistics.

3. Analysis of the results of epidemiological studies and clinical manifestation observed in congenital heart disease among the neonates

3.1 Significance of congenital heart disease (CHD) in the structure of morbidity and mortality in the Odessa region

Although many newborns with congenital heart disease are symptomatic and identified soon after birth, others are not diagnosed until later. In infants with potentially life-threatening lesions (Critical Congenital cardiac defects/ CCCD), the risk of morbidity and mortality increases when there is a delay in the diagnosis and timely referral to a tertiary center with expertise in treating these patients.

Estimated prevalence of CHD in the Odessa region is 4-10 per 1000 newborn babies and among the preterm infants (gestational age less then 37 weeks), the rate is two to three folda higher than that is found in term infants. Presence of an isolated CHD comprises almost 7-8% of the neonatal mortality. As an absolute factor responsible for neonatal mortality, CHD constituted in the year of 2007 0,56‰ and in 2011 0,45‰. Proportional indicator of the neonatal mortality rate in the presence of an isolated CHD comprises 67‰. The secreasing neonatal mortality rate due to CHD can be reasonably attributed to the availability and more rapid access to the emerging cardio-vascilar intervention facilities in the odessa region in the recent past. During the laast 5 years in the Odessa region the incidence of congenital malformations constituted almost about 9% in the neonatal period.

Congenital Heart Defects (CHD) still remain the most common developmental anomaly. Among the predominant causes of neonatal mortality, the bulk of congenital malfomiations always occupied the second place and it contributed nearly 18-21% of the total neonatal mortality rate in the region. While considering the in-depth structure of neonatal mortality, CHD seemed to be the most common pathology (7-8%) among all isolated congenital malfonnation. At the same time absolute

number of deaths from CHD is reduced significantly: in 2007 - 0,56 ‰, and in 2010 - 0,45 ‰. The proportional mortality from isolated cases of CHD in the populations of Odessa region for the period from 2007 to 2010 is 67%. 2011 Comparison of data from the study group neonates and healthy babies showed no difference in gender distribution (OR 1.24, 95% CI 0,5-2,9). The children with CHD had significantly lower gestational age (37.5 and 39.5 weeks of'GA, respectively, p <0.05) and lower birth weight (2.51 and 3.89 kg respectively, p <O.OI). At the same time no significant differences had been revealed between the compared groups concerning the criteria of prematurity and the Apgar score. [1,3]

The spectnim of CHD found within the study group is described below: Ventricular Septal Defect (VSD: 21 - 35%), Patent Ductus Arteriosus (PDA: 10 17%), Patent Foramen Ovale (PFO 8 - 13%). Alrial Septal Defect (ASD: 1 - 1.7%), Transposition of Great Arteries (TOA: б - 10%), Coarctation of the Aorta (CoA;46.7%), Hypoplasric Left heart Sydrome (HSLS: 3 - 5%), Complete Atrioventncular Communication (AVC : 2 - 3.3%), Pulmonary Atresia (PA : 2 - 3.3%), Stenosis Aortic Valve (AVS: 1 - 1.7%), Pulmonary Stenosis (PS: 1- 1.7%), Anomaly of Ebstein (EA:l- 1.7%).

Among the neonates who were included in the study group of critical congenital heart disease (CCHD, n=20); among them 7 newborn babies – were alive and 13 newborns have died from the following CHD: Transposition of great arteries (TGA 3), Truncua Arteriosus (TA 2), Hypoplastic left heart syndrome (HSLS 2), Stenosis of aortic valve (AVS 2), Aortic valve atresia (AVA 1), Critical Coarctation of the Aorta (CCoAl), Total Anomalous Pulmonary Venous Return of (TAPVR 1), and Anomaly of Ebstein (EA 1). Depicted in table № 1.

Table № 1

Mortality Due to Isolated Congenital Heart Diseease in the Neonatal Period:
International

Classification of Diseases (ICD-10)	Diagnosis	Year	
		2010	2011
Q 20.0	Common Arterial Tmnk (Truncus Arteriosus)	1	1
Q 20.3	Discordant ventriculoarterial	3	

	Connection Transposition of Great Vessels (complete)		
Q 23.4	Hypoplastic Left Heart Syndrome	2	
Q 25.1	Critical Coarctation ofAorta	1	
Q 26.2	Total Anomalous Pulmonary Return		1
Q 23.0	Aortic Valve Stenosis		2
Q 23.0	Atresia of Aortic Valve		1
Q 22.5	Anomaly of Ebstein		1
Total CHD (n=13)Detected		7	6

3.2. Characteristics of Congenital Heart Disease (CHD) according to the International Disease Classification (ICD-10: Version: 2010)

The International Classification of Diseases (ICD) is the standard diagnostic tool for epidemiology, health management and clinical purposes. This includes the analysis of the general health situation of a definite population. It is used to monitor the incidence and prevalence of diseases and other health problems.

According to the ICD-10; Version 2010 the congenital malformations of the circulatory system is incorporated within the following codes described between Q20-Q28. Although as per the ICD criteria congenital heart disease had not been classified in to Critical or Non-critical sub entities but for all practical purpose while analyzing the neonatal death due to CFID in the Odessa region, critical diseases (duct dependent systemic or pulmonary CHDs) had been given specific importance because they always need urgent strategical intervention. We have analyzed the details of the autopsy reports of all thirteen (13) patients who died due to CCHD and classified them according to the ICD-10. Depicted in table № 2.

Table № 2

Total CHD (n=60) encountered within our study group:

CHD Diagnosed	N	%
Complete AVC	2	3,33%
TGA	6	10%
VSD	21	35%
PDA	10	17%
AoV Stenosis	1	1,66%
PFO	8	13%
II ASD	1	1,66%
CoA	4	6,66%
PA Stenosis	1	1,66%
HLHS	3	5%
EA	1	1,66%
PA Atresia	2	3,33%
Total	60	100%

3.3 Comparative Characteristics of All the Three Study Groups:

Statistical findings are represented I table № 3

Table 3

Comparative Characteristics of all the three Study Groups

Criteria	III (16) & I (40)		II (10) & I (40)		II (10) & III (16)	
[Neonatal]	CI	OR	CI	OR	CI	OR
Preterm	0,1-0,92	0,11	0,16-3,19	0.71	0,56-73,35	6.43
IUGR	0,1-15	1,3	0,17-25,93	2,11	0,09-30,06	1,67
Sat < 80%	5,58-131,96	27,13	7,04-345,22	49,33	0.28-11,87	1,82
Perinatal Asphyxia	0,13-2,24	0,54	0,1-3,16	0,58	0,35-7,96	1,08
Feeding: Breast	0,05-0,85	0,2	0,04-1,2	0,23		
Gavage	0,33-4,24	1,2	0,42-7,44	1,76	0,15-7,96	1,08
Parenteral	0,86-94,24	9	0,79-120,96	9,75	0,28-7,36	1,47
Severity of the General Condition: Critical	1,03-25,85	5,17	0,39-7,66	1,72	0,15- 7,96	1,08
Moderately severe	0,17-5,77	1,0	0,08-7,52	0,78	0,04-2,48	0,33
Cyanosis	1,29-15,23	4,43	1,19-22,4	5,16	0,06-9,88	0,77
Respiratory failure	0,77-10,37	2,83	0,2-6,79	1,18	0,23-5,8	1,16

Tachicardia	1,47-50,8	8,65	0,58-39	4,75	0,06-2,65	0,42
Anaemia	0,34-5,25	1,33			0,08-3,59	0,55
Condictivity disturbances	0,08-8,55	0,82				
Therapeutic measures: Diuretics	2,06-44,58	9,59	0,44-21,58	3,08	0,05-2,02	0,32
Inotrops	0,8-21,03	4,11	0,44-21,58	3,08	0,11-5,11	0,75
PGE 1					0,02-0,95	0,15
Oxygen	2,62-83,47	14,78			0,17-4,27	0,86
[Maternal]:	CI	OR	CI	OR	CI	OR
BOH	0,27-2,97	0,9	0,02-1,45	0,17	0,02-1,85	0,19
Threatened abortion in 1st Trimester	0,34-7,73	1,62				
ARI	0,28-6,01	1,31	0,24-8,37	1,42	0,15-7,96	1,08
Co-morbid Conditions	0,05-4,34	0,47	0,97-22,53	4,67	0,92-109	10

3.3.1. Descriptive Analyses of Comparative Characteristics of All the Three Study Groups

According to our study during the period of 2010-2011 in Odessa region the incidence of CHD found to be 18 per 1,000 live births. A significant part of the CHD belongs to critical heart defects (CCHD), viz. Hypoplastic left heart (7.57% of all CHD), Complete atrioventricular canal (3.03%), Double outlet right ventricle (DORV) (1.51%), Single ventricle in association with other heart diseases (1.51%), TGA combined with ventricular septal defect (3.03%), VSD combined with ASD and PDA (6.06%). Isolated VSD, and are dominated (24.24%) amidst of all CHD, in combination with other heart detects 15.15%. Isolated PDA constitutes 12.12% Haemodynamically significant PDA is 25% of the total CHD encountered; PDA in combination with other CHD (6.06%). Malformations like Anomaly of Ebstein (1.51%), Coarctation of aorta (3.03%), Pulmonary stenosis (1.51%), Cardiac distopy in conjunction with CHD (1.51 %) are relatively rare.

The clinical manifestations of CHD in all newboms can be divided into three groups:
Group 1 - asymptomatic in the newborn period (hemodynamically insignificant PDA. isolated septal defects without HLHS, mild coarctation of the aorta, moderate valvular stenosis).
Group 2 - symptomatic in the newborn period, but without heart failure. CHD can be manifested with cardiac murmur, tachycardia, tachypnoea, central cyanosis (combined CHD with adequately functiomng compensated shunts).

Group 3 –symptomatic with heart failure in newborn period (with clinically evident signs of cardiac failure: dyspnoea, oedema, diminished urine output, marked central cyanosis, severe general condition). Critical CHD viz. hypoplastic left (or right) heart syndrome, TGA, valvular atresia, critical CoA, combined CCHDs.

The outcome of CHD described in group one is always favourable. These detects usually do not require medication and emergency surgical intervention. If needed planned operative measures are taken. Neonates included within group II require longer observational care, therapeutic measures (diuretics, cardiac glycosides, ACE inhibitors), individual approach of surgical intervention (depending on severity and complication of the underlying CHD). Neonates belonging to the IIIrd group require intensive care depending on the severity of the disease and often need urgent medical interference (diuretics, cardiac glycosides prostaglandins, inotrops, oxygen therapy or mechanical ventilation). Emergency surgical interventions are almost always required. Among the neonates of group one (n=40) CHD with enrichment of pulmonary circulation (predominantly a left to right shunt) are commonly encountered without any symptoms of heart failure. Cardiac malformations are enlisted in table № 4,5&6.

Table № 4.

Structure of CHD in the group one (n=40).

CHD	N
Ventricular Septal Defect(VSD)	16
Patent Foramen Ovale(PFO)	7
Patent Ductus Arteriosus(PDA)	5
Patient foramen ovale with conduction disturbance	2
Secondary atrio ventricular defect (SAVD)	2
PDA with VSD	3
Complete atrioventricular canal	1
Dextrocardia with VSD	1
Secondary atrial septal defect (II ASD with PDA)	1
VSD and ASD	1
Isolated stenosis of pulmonary artery	1

Table № 5

Structure of CHD in the group 2 (n=10).

CHD	N
Haemodynamically Significant PDA	2
Hypoplastic Left Heart Syndrome	2
Anomaly of Ebstein	1
Complete AVC	1
Atresia of Pulmonary Artery Type «A»	1
PFO	1
DORV	1
CoA	1

Table № 6

Structure of CHD in the group Three (n=16).

CHD	N
TGA without VSD	3
HLHS	3
TGA with VSD	2
Critical CoA	1
PDA	1
Single Ventricle (SV)	1
Atresia of Pulmonary Artery with VSD	1

For the detection of high risk group among the neonates having CHD, pulseoximetry screening test had been conducted. Overall objective assessment of the following parameters were done: evaluation of general condition, analysis of clinical and laboratory findings, consideration of the therapeutic intervention and maternal anamnesis.

And finally below mentioned factors were analyzed: Gestational age and maturity of the neonate, SaO2 level, History of perinatal asphyxia, Feeding types, breast, enteral or parenteral), the severity of general condition (critical or moderate), presence of cyanosis, respiratory failure, tachycardia, arrhythmias, anaemia. Therapeutic interventions were also taken into account (diuretics, oxygen, motropic support, and need for PGE1).

In our study the following details of the maternal anamnesis were also included: bad obstetric history, risk of threatened abortion in the first trimester, respiratory viral infection, and presence of co-morbid conditions during pregnancy.

These data were statistically analyzed. Statistical comparison among the study cohorts were carried out to determine the diagnostic value of pulse-oximetry screening, indications for further in-depth investigations (echocardiography, chest x-ray etc.), and also to identify the factors, which substantially differentiates one group from another.

According to the results of comparative statistical analysis is suggestive of:

1 - factors that characterize each group

2 - factors that are common to all groups

3 - factors that have no statistical significance

For the all three group of neonates most characteristic (statistical significance in decreasing order):

- Oxygen saturation below 80% (CI 5,58-131,96; OR 27,13)

- Need for prostaglandins, sign that is present only in this group.
- Oxygen therapy (CI 2,62-83,47; OR 14,78)
- Diuretic therapy (CI 2,06-44,58; OR 9,59)
- Parenteral nutrition (CI 0,86-94,24; OR 9)
- Tachycardia (CI 1,47-50,8; OR 8,64)
- Critical general condition (CI 1,03-25,85; OR 5.17)
- Cyanosis(CI 1,29-15,23; OR 4.43)
- Inotropic support (CI 0,8-21,03; OR 4,11)

Such type of factorial distribution explains the pathogenesis of CHD in this group. Since these defects occur on the background of heart failure, with symptoms of hypoxaemia, newborn babies requiring intensive care from the first day (hours) of life and with an oxygen saturation below 80%, will be of great importance during the early neonatal period for the detection of CHD.
Prostaglandin is indicated in case of critical congenital heart defects. Our 3 group included neonates with such type of CHDs. So, this factor remains the principal criterion for the group III, as well as determinant of severity.
Identification of these factors within the newborn population suggestive of poor prognosis. Other factors have no statistical significance for the group. For the group 2 most characteristic remains the following factors, (statistical significance in decreasing order):
- Saturation below 80% (CI 7,04-345,22; OR 49,33)
- Oxygen therapy (CI 1,89-84,97; OR 12,67)
- From the maternal history - comorbidities (CI 0,92-109; OR 10)
- Parenteral nutrition (CI 0,79- 120,96; OR 9,75)
- The degree ofprematurity (CI 0,56-73,35; OR 6,43)
-Cyanosis (CI 1,19-22,4; OR 5,16)
The factorial distribution pattern in group 2 also explains the pathogenesis of CHD within this group. Or saturation below 80% within group 2 in companson to 1st and 3rd group is highly significant. CHD in 2nd group involves a bidirectional shunts through duct and septal defects. Saturation below 80% will be most important indicator for group 2, than group 3, in association with CCHD, as haemodynamic significant mixing of blood is achieved through unidirectional compensating shunts in case of CCHD. This also explains the importance of oxygen therapy ans parenteral nutrition. Maternal comorbid condition in the presence of preterm birth remains the major risk factor for the development of complications related to immaturity of the respiratory

system, which also explains the importance of oxygen therapy.

Cyanosis and tachycardia are also pathogenctically related to the above mentioned factors. Since the defects of this group are more compensated than the lesions of 3rd group, the importance of treatment of heart failure within this group is less pronounced. Identification of such factors among the neonates indicate the presence of a significantly complex CHD.

The first group characterizes the absence of the features listed above, except for the saturation level below 80%, as this group comprises CHDs, prone to longer period of compensation, without clinical manifestations (cyanosis, tachycardia and tachypnoea). Neonates within this group do not require intensive care and urgent surgical intervention. 02 saturation below 80% (compared with group III CI 5,58131,96; OR 27,13; and with group II CI 7,04-345,22; OR 49,33). Left to right shunting explains the haemodynamical pathogenesis of these CHD. On the early neonatal life, due to the presence of physiological pulmonary hypertension, pressure in the right ventricle is variable. When the systolic pressure in the RV is increased, right to left shunting takes place through the physiologically functioning PFO, resulting in lower SaO2. Therefore, this factor is characteristic for the neonates in Group 1. Oxygen saturation below 80% significantly indicates a likelihood of CHD. The common factor for the three study groups remains saturation below 80%. Factors such as intrauterine growth retardation, perinatal asphyxia, breastfeeding feeding, Gavage feeding, General condition with moderate severity, anaemia, arrhythmias, Bad obstetric history (BOH), threatened abortion in the first trimester and respiratory viral diseases during pregnancy do not show any statistical significance.

3.4. Slatistical Comparison of the Neonates with CHD, According to the Disease Manifestation (Comparative Analysis of Clinical and Anamneslic Findings).

Heuristically and also by the analysis of literature review sources for the detection of the risk factors (to analyze the predispositional monofactor of CHD) newborn babies were outlined according to the following symptoms and condirions: the presence of different types of maternal infections in early pregnancy, TORCH-infections. Maternal history of CHD, Diabetes, Obesity, Harmful habits. Bad obstetric and gynecological history (Pelvic inflammatory disease, Spontaneous abortions, Child deaths in the perinatal period).

As a result of the predispositional monofactorial analysis we found that the following factors are statistically significant: Maternal history of CHD (OR 13.5, 95% CI 1,39-107,2), Bad obstetric and gynecological history (OR 1.2, 95% CI 1,09-6,4), the presence of TORCH (OR 3.71, 95% 1,7-20,2).

We have also analyzed the following unfavorable outcome predictors of CHD during the neonatal period: Prematurity, ARI in the first trimester of pregnancy, the presence of Comorbid conditions, Hypoxic-Ischemic Encephalopathy (HIE). But Maternal smoking, Seasonal viral respiratory infections during the early pregnancy, Chronic pyelonephritis, Gender of the child, Prematurity and IUGR didn't show any statistical significance. Any case of Maternal history of Diabetes and Obesity were not encountered within our study group. During our study, based on the anamnestic, clinical and instrumental findings we had indentified a total number often parameters which were considred to be the determinant factors for the outcome of congenital heart disease. Deterioration of the general condition (rapid progression of seventy due to CHD) of the neonates soon after the birth were also taken into account depending upon the critical and non-critical natute of the malformation.

These defining factors (as prognostic markers of disease) are described below:

• Rapid onset of criticality (severity of the general condition in the early neonatal period)

1st day of life

2nd day of life

- Cyanosis (Central)
- Tachypnea
- Tachycardia
- Hepatomegaly
- Diuresis
- Oedema
- Sa02 ↓ 80% in room air (i.e. Fi02 - 0,21%)
- Murmur
- Anaemia

An additional factor (i.e. Gestational Age) was also considered to evaluate if, GA has got no prognostic implication in the presence of congenital heart disease during the neonatal period. After identifying these prognostic markers we have devided the cases of congenital heart diseases detected within our study groups according to the outcome whether favourable or unfavourable and alculated the Odds Ratio and Confidence Interval. Amidst them the following statistically significant clinical

predictors of poor prognosis were identified on the 1st day of neonatal life in the presence of Congenital Heart Disease:

- SpO2 ↓80% - Odds Ratio = 48.9 (95% CI, 5,57-428)
- Central cyanosis - Odds Ratio = 29.6 (95% CI 6,5.134,5)
- Tachycardia - Odds Ratio = 6.5 (95% CI 1,1-37,2).

After analyzing the all echocardiographic evalution made within our study group, we have also indentified the below mentioned unfavourable predictors of poor prognosis (ultasonographic markers) which is characterized of CHD during the neonatal period:

- Reduction of ventricular myocardial contractility,
- Dilatation of the heart chambers or the sharp decrease in the size of cardiac chambers,
- Severe Pulmonary Hypertension,
- Hypoplasia of valves and great vessels,
- Dysfunction of the compensatory shunts,
- The presence of pathological shunts, and
- Reduced blood flow in the abdominal aorta.

Proper identification of the risk factors of CHD is a definite indication for performing an early neonatal screening: pulse oxymetry and echocardiography (if available) before the discharge of the child from the the health care facility. Unfavourable course predictors can also help to determine the optimal treatment measures ofCHD during the neonatal period.

4. The Screening Method and Results of Population-based Pulse-oximetry For the Early Detection of Congenital Heart Defects During Neonatal Period:

4.1 Description of the Pulse-oximetry Screening Methods:

Study population:

Between 19 th January 2011 to 31 st May 2011, 375 babies born at Odessa Oblast Perinatal Centre were included in a prospective obsevational study for optimising screening performance with pulse oximetry conducted by clinical research fellow of the First Department of Paediatrics, Neonatology and Bioethics of Odessa National Medical University. Prospective screening of the babies were carried out in well baby nurseries, post-natal wards and in the neonatal intensive care unit.

Four (4) neonates were excluded from the study out of the total number of observed patients (i.e. 375) for having severe respiratory pathology (RDS) and/or with very critical condition.

Screening study:

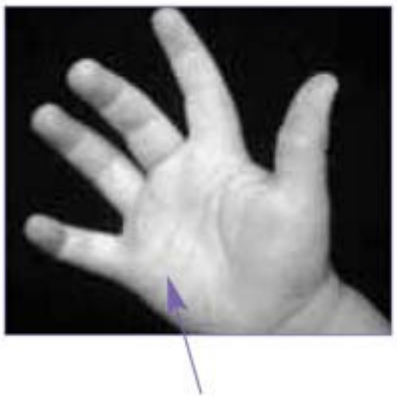
Screening neonates with non-invasive measurement of oxygen saturation has been proposed as an aid for early detection of duct dependent circulation.
We evaluated strategies to maximise sensitivity while minimising the false positive subjects in a screening test for duct dependent circulation with a new generation oximeter (Massimo Set, Rad-87 Pulse Co-Oximeter – Horizontal,USA) which measured functional oxygen saturation preductally (in right hand) and postductally (in right foot). We arrived at optimal screening cut-off values of <95% saturation OR, >3% difference between right hand and foot.
We also found that the type of oximeter used had a significant effect on both the detection rate and false positive rate.

The infants' age at screening, gender, and mode of delivery (caesarean section or vaginal) and the over all technical quality of the measurement (optimal or non-optimal includinging the co operativeness of the neonates during the procedure) were recorded on a reporting form (part of the standardized study protocol).

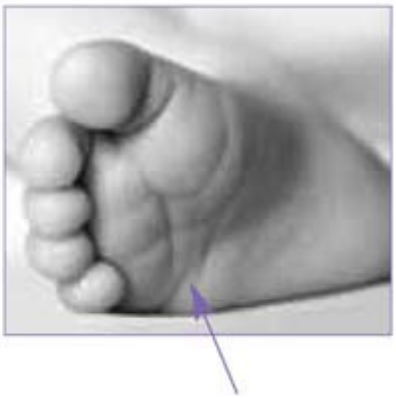
4.1.2 Screening Method:

Proper Pulse Oximetry Probe Placement:

1. Select application site on the outside, fleshy area of the infant's hand or foot.



RH Application Site



Foot Application Site

2. Place the photodetector portion of the probe on the fleshy portion of the outside of the infant's hand or foot.

3. Place the light emitter portion of the probe on the top of the hand or foot. Place the photodetector directly opposite of light emitter, on the bottom of the hand or foot.

4. The photodetector and emitter must be directly opposite each other in order to obtain an accurate reading.

5. Secure the probe to the infant's hand or foot using the adhesive or foam tape. (It is not recommended to use tape to secure probe placement).

4.2 Results of the Pulse-oximetry Screening :

Evaluation of the diagnostic value (i.e. speficitty and sensitivity) of newborn screening for the presence of congenital Heart Disease using pulse oximetry is shown in Table. A.

Analysis of the diagnostic value of screening has demonstrated high specificity while the SpO2 <95% in the right hand and foot but showed lack of adequate sensitivity.
Which means a positive screening result (SpO2 <95%) neonates likely to have congenital heart disease, while a negative test result (SpO2 ≥ 95%) did not exclude the possibility of a congenital heart disease in the same population.
Based on the likelihood ratio for a positive result (LR+), an affirmative result in hand and foot carries equal statistical significance to establish the post-test probability of disease (PPD).

Differences between SpO_2 in the arm and foot have also demonstrated a high diagnostic specificity, but significantly lower diagnostic sensitivity, this result moderately influences the post-test likelihood of disease. It should be noted that differences in SpO_2 in the hands and feet are more likely related with coarctation of aorta. These data coincide with a number of studies that indicate the need for mass screening of newborns to detect congenital heart disease with the help of pulseoximetry.

4.3 Evaluation of the Diagnostic Value of Pulse oximetry Screening During Neonatal Period for the Early Detection of Congenital Heart Disease :

Table. A:

Parameter	Dspe (95 % CI)	Dsen (95 % CI)	PPV/VP+ (95 % CI)	NPV/VP- (95 % CI)	LR+ (95 % CI)	LR- (95 % CI)
Foot: SpO2 < 95 %	0,51 (0,32–0,75)	0,99 (0,98–1,0)	0,92 (0,78-1,0)	0,94 (0,9–0,97)	83,3 (13,8-503,8)	0,49 (0,34-0,72)

Hand: SpO2 < 95 %	0,45 (0,25–0,64)	0,99 (0,98–1,0)	0,86 (0,67-1,0)	0,94 (0,91-0,97)	49,8 (11,1-223,4)	0,56 (0,39-0,79)
SpO2 Foot < SpO2 Hand = >3 %	0,27 (0,11–0,44)	1,0 (1,0–1,0)	1,0 (1,0–1,0)	0,91 (0,86-0,94)	0	0,73 (0,58-0,92)

From the popularion based screening it was found that the statistically significant clinical predictors of poor prognosis in Congenital Heart Disease (CHD)on the first days of life were:

- SpO_2 below 80% - 48.9 OR (95% CI, 5,57-428) and beside pulse-oximetry other two major clinical parameters remaied
- Central cyanosis - OR 29.6 (95% CI 6.5 - 134.5) &
- Tachycardia - OR 6.5 (95% CI 1,1-37,2).

Tachypnoea, indication for early initiation of mechanical ventilation, oedema, hepatomegaly, and cardiac murmur showed no statistical significance between the groups with favourable and unfavourable disease course.

4.4 Performing Pulse Oximetry within the Neonatal Population:
(Outline of the Research Protocol for Newborn Screening)

Pulse Ox – Do's:

1. If disposable pulse ox probes are in use, then a new, clean probe for each infant should be used. If working with a reusable pulse ox probes, the probe must be clean with recommended disinfectant solution between each infant.
   Dirty probes can decrease the accuracy of your reading and can transmit infection. A disposable wrap should be used to secure the probe to the site.
2. The best sites for performing pulse ox on infants are around the palm and

the foot. An neonatal pulseox probe (not an adult pulse ox clip) should always be used for infants.

3. When placing the sensor on the infant's skin, there should not be gaps between the sensor and the infant's skin. The sides of the probe should be directly opposite of each other.
4. Nail polish dyes and substances with dark pigmentation (such as dried blood) can affect the pulse ox reading. Assure that the skin is clean and dry before placing the probe on the infant. Skin color and jaundice do not affect the pulse oximetry reading.
5. Movement, shivering and crying can affect the accuracy of the pulse ox reading. Ensure that the infant is calm and warm during the reading. Swaddle the infant and encourage family involvement to promote comfort while obtaining the reading. If possible conduct screening while the infant is awake.
6. Pulse oximeters have different confidence indicators to ensure that the pulse ox reading is accurate. Determine the confidence indicators for the pulseoximetry equipment that you are using.

7. If an infant requires pulse ox monitoring for an extended amount of time, assess the site where the probe is placed at least every two hours. Monitor for signs of irritation and burning of the skin.

Pulse Ox – Don'ts :

1. Never use an adult pulse ox clip when obtaining a pulse ox reading for a neonate. Using an adult clip on an infant will give you an inaccurate reading.
2. Blood flow is needed to obtain an accurate pulse ox reading. Never attempt to obtain a pulse ox reading on the same extremity that you have an automatic blood pressure cuff.
3. Bright or infrared light, including bilirubin lamps and surgical lights, can affect the accuracy of the reading. Ensure that the infant is not placed in bright or infrared light while pulse ox is being performed. The pulse ox probe may be covered with a blanket to ensure that extraneous light doesnot affect the accuracy of your reading.

4. Do not use tape to apply the pulse ox probe to the infant's skin.

Pulseoximetry Caution:

5. The pulse is needed to determine the oximetry reading. Pulse ox is not accurate if the patient is coding or is having a cardiac arrhythmia.

6. Pulse ox readings are not instantaneous. The oximetry reading that is displayed on the monitor is an average of readings over the past few seconds.

Supplies for screening:

• Pulse Oximeters:
– At least one motion-tolerant pulse oximeter to be used for screening,
– One motion-tolerant pulse oximeter for back-up.

• Infant Disposable or Reusable Pulse Ox Sensors:
– If using disposable sensors, one disposable sensor for every infant screened,
– If using reusable sensors, one reusable sensor for each pulse oximeter,
– Also consider additional reusable sensors for back-up
– Disinfecting agent recommended by pulse oximetry equipment manufacturer
– One disposable wrap per infant screened to secure sensor to hand or foot.

• Rolling Cart for Supplies,
• Data Collection Forms,
• Dedicated medical personnel to perform screening,
• Blankets for warming the infant and blocking extraneous light.

Screening Interpretation implications:

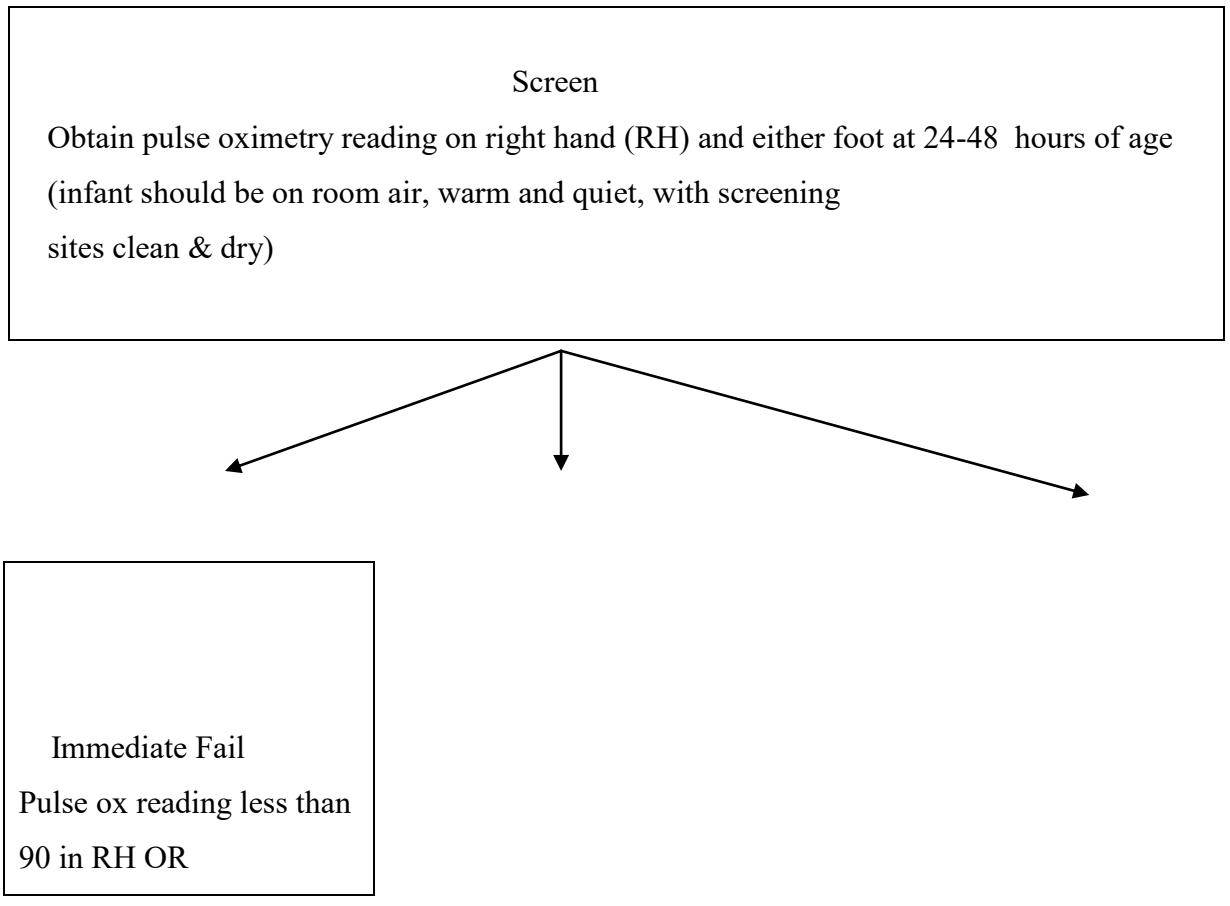
– Pulseoximetry screening algorithm should not take the place of clinical judgment

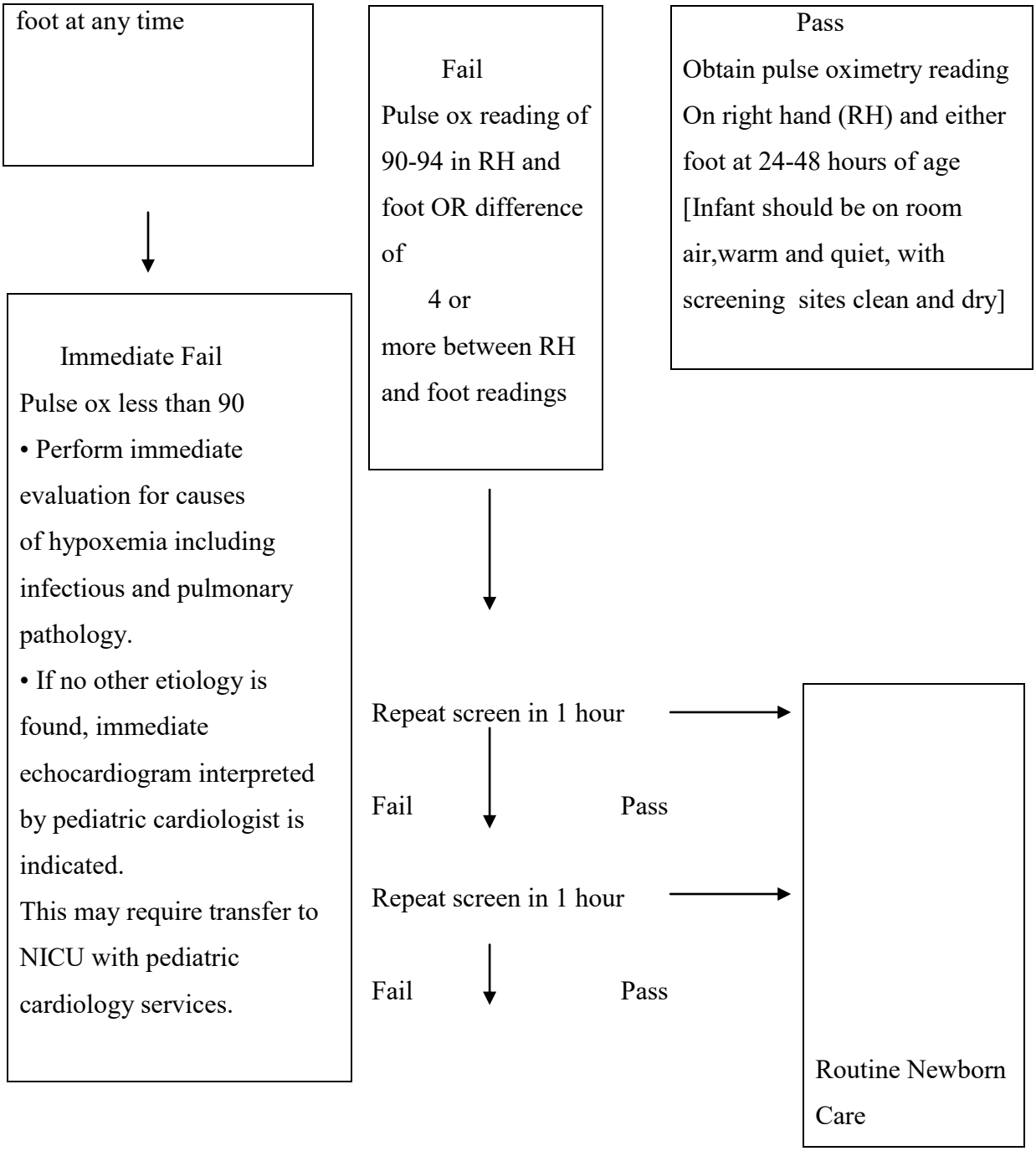
or customary clinical practice.

– A negative screen does not rule out heart disease.

– Optimal results are obtained using a motion-tolerant pulse oximeter that reports functional oxygen saturation, has been validated in low perfusion conditions, has been cleared by the FDA for use in newborns, has a 2% root mean-square accuracy, and is calibrated regularly.

Pulse-oximetry Screening Algorithm:




foot at any time
Fail
Pulse ox reading of 90-94 in RH and foot OR difference of 4 or more between RH and foot readings
Pass
Obtain pulse oximetry reading On right hand (RH) and either foot at 24-48 hours of age [Infant should be on room air,warm and quiet, with screening sites clean and dry]
Immediate Fail
Pulse ox less than 90
• Perform immediate evaluation for causes of hypoxemia including infectious and pulmonary pathology.
• If no other etiology is found, immediate echocardiogram interpreted by pediatric cardiologist is indicated.
This may require transfer to NICU with pediatric cardiology services.
Repeat screen in 1 hour
Fail
Pass
Repeat screen in 1 hour
Fail
Pass
Routine Newborn Care

Failed Screen

Pulse Ox 90-94 or RH/foot difference ≥ 4 x 3

• Perform comprehensive evaluation for causes of hypoxemia including infectious and pulmonary pathology.

• If no other etiology is found, consultation with pediatric cardiology or neonatology is indicated to arrange for a diagnostic echocardiogram to be interpreted by a pediatric cardiologist. This may require telemedicine, transfer to an NICU with pediatric cardiology services, discussion with cardiology services, or discussion with cardiology to schedule a timely outpatient echocardiogram.

5. Inference.

Congenital Heart Disease (CHD) still remains the most prevalent malformation among the all anomalous congenital defects in the Odessa region. Although the neonatal mortality rate (NMR) due to CHD had been significantly declined during the last 5 years, this form of congenital malformation is responsible for 8% of the over all neonatal mortality in the region and undoubtedly plays an important role on the dereasing trend of the NMR in the Odessa region in the recent past.

Isolated CHD is responsible for 7-8% of all neonatal mortality. The absolute mortality rate from CHD in last 5 years decreased from 0,56 %o to 0,45 %o; and Proportional indicator of the neonatal mortality rate in the presense of an isolated CHD comprises almost 67%.

One of the major risk factor for the fonnation of CHD remains TORCH infection of mother (OR 3.71), presence of maternal CHD (OR 13.5) and BOH (Bad Obstetric History, OR 1.2).

Unfavorable course predictors of CHD during the neonatal period were prematurity, ARJ in the first trimester of pregnancy, the presence ofcomorbid conditions, Hypoxic-Ischemic Encephalopathy (HIE).

Screening of the neonates by means ofpulseoximetry [measuring the pre and post ductal oxygen saturation in right hand and right foot] proved to have high sensitivity for the detection of Congital Heart Disease [in the absence of respiratory pathology], but the normal level ofoxigen saturation [i.e. SpO2> 95%] does not exclude the probablity ofCongital Heart Disease (CHD).

If post-ductal saturation is higher than the pre-ductal [i.e. reverse differential cyanosis] that might suggestive of:

- TGA with CoA or TGA with IAA,
- TGA with supersystemic pulmonary vascular resistance.

On the other hand if pre-ductal saturation is higher than post-ductal saturation [i.e. differential cyanosis] it is highly indicative of left heart abnormalities (such as aortic arch hypoplasia, critical aortic stenosis, intermpted aortic arch) or persistent pulmonary hypertension (PPHN).

Comparative measurement of SpO2; in the right hand and foot may be considered as an additional tool to elicit the presence of CHD among the newborn population but without the proper clinical correlation, it alone could never be the deciding modality to establish the final diagnosis.

<u>Practical Implication.</u>

Our study summerizes the results of epidemiological study of congenital heart diseases among the newboms. Also identifies the risk factors and predictors of poor prognosis. Shouts attention for the necessity of mass screening of newborn babies by pulseoximetry before the discharge from the maternity hospitals which is simple, cost benificial and effective.

Optimization of early diagnosis and management of CHD could play a significant role in the reduction of neonatal mortality rate. Proper identification of the risk factors of CHD is a definite indication for performing an early neonatal screening: pulse oxymetry and echocardiography (if available) before the discharge of the child from the the health care facility.Unfavorable course predictors can also help to determine the optimal treatment measures of CHD during the neonatal period.

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