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Routine Pulse Oximetry Screening to Detect Critical Cyanotic Congenital Heart Disease in Neonates After Birth – A Developing Country Perspective & Experience

By R. Kishore Kumar, MD, FRCPCH, FRACP; Arvind Shenoi, MD; Kishore Vrajananda Yerur, DCH, MRCPCH; Syed Tajamul, DCH, MD; Prakash Kini, DGO, MD

Abstract

Objective

Pulse Oximetry in newborns to detect the Critical Cyanotic Congenital Heart Diseases has become a standard of care in many developed countries after recent guidelines. We undertook this to see if it is feasible in Indian circumstances and also wanted to see the cost implications of the same.

Setting

Tertiary Maternity Hospitals in Bangalore, India.

Participants

All babies born above 36 weeks at the hospital and were with the mothers during the first few days – and not requiring Neonatal Intensive Care Unit (NICU) admission.

Main Outcome Measures

The economic feasibility of the results of our protocol is reviewed after 2 years.

Results

Screening by Pulse Oximetry was done for a total of 22,601 neonates between June 2012 and Oct 2016 (study period). Thorough clinical examination done by the neonatologists for the 14 neonates who failed screenings, revealed that three babies had a pulmonary condition requiring treatment (false positive cases) and 11 babies were investigated with an Echocardiography by a Paediatric Cardiologist. One infant had a PDA with no other abnormalities, one had a VSD with a small PDA, but no other abnormalities, and the remaining nine infants were diagnosed with CCHD: three were found to have Transposition of Great Vessels (TGV) (3); two were found to have Total Anomalous Pulmonary Venous Drainage (TAPVD) (2); one baby was found to have Fallot's Tetralogy (TOF), one baby had a VSD, an ASD and Patent Foramen Ovale with pulmonary hypertension; one baby had severe pulmonary hypertension (PAH) and two babies had pulmonary stenosis (PS).

Conclusion

Our data shows evidence for Pulse Oximetry screening of apparently healthy newborns to become a standard of care in India like many developed countries and is very cost effective, and is affordable.

Key Words: Congenital Heart Disease (CHD), Critical Cyanotic Congenital Heart Disease (CCCHD), newborn, Pulse Oximetry, screening.

What Is Already Known on this Topic:

1. Pulse Oximetry screening has been shown to improve the prognosis of early-diagnosed Critical Congenital Cyanotic Heart Disease in newborn babies.
2. Barriers to implementation include concerns about increased workload on echocardiography services.
3. Screening programs are being implemented in most developed countries.

What this Paper Adds:

1. Pulse Oximetry screening does improve early diagnosis of CHD with minimal increase in cost and the burden on echocardiography services.
2. It is equally effective in improving early diagnosis of other, mainly respiratory, pathologies.
3. There is enough evidence to suggest a national recommendation for Pulse Oximetry screening in India.

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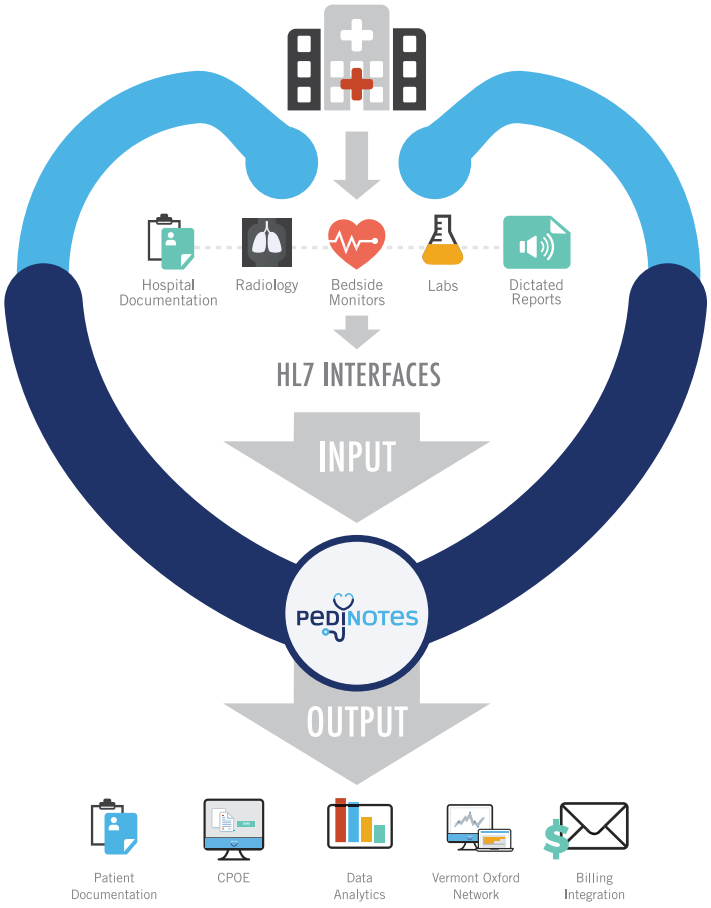

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Congenital Heart Disease is an important cause of death and morbidity in early childhood with a prevalence of 5-10 per 1000 live births worldwide.[1] One-fourth of these have major CHD (defined as requiring surgery or catheter intervention in the first year of life). In India, heart disease in young children accounts for more than 10% of all childhood deaths due to late presentation or diagnosis.[2,3]

Early diagnosis can prevent progression to cardiac failure, cardiovascular collapse, neurological sequelae and death.[2,3] Currently, screening for CHD relies on antenatal ultrasonography in the mid-trimester and post-natal clinical examination. Antenatal scans have a diagnosis rate of up to 44%, while newborn examination diagnoses are less than 50% of CHD and have a false positive rate of 1.90%.[4,5] Pulse Oximetry screening of newborns has been shown to be a non-invasive test that increases the ability to identify infants with major CHD before clinical presentation with collapse, which may result in long-term complications.[2,5]

In 2012, a chain of tertiary maternity hospitals in India reviewed the published evidence of the benefit and decided to implement this practice into routine care, especially after one of their parents was upset and they alleged that we had 'missed' diagnosing their baby with CCHD at birth. These parents were quite upset when they learned that a simple non-invasive test could have helped their baby to be diagnosed at birth instead of at the age of 2 ½ months when the baby was diagnosed because of a murmur. We present our Indian experience.

This paper describes a post-implementation review of the first 52 months of Pulse Oximetry screening of well newborns at these hospitals. The aim is to describe the implementation of the screening programme and review whether the outcomes were consistent with those described in the literature in our setting and the cost implications for doing that.

Methods

The study population included all babies born at the four maternity tertiary care hospitals between June 2012 and October 2016. A group of tertiary maternity hospitals {four of which are located in Bangalore (one each at Old Airport Road, Malleshwaram and two in Jayanagar)}, delivering over 5,000 babies a year, provide Maternal Fetal Medicine service, including screening for high-risk births and cardiac screening.

Pulse Oximetry Screening

Screening was initiated in June 2012, in all the four hospitals after deliberations of the evidence available so far in the literature and discussions among peers as to its feasibility. Pulse Oximetry screening was conducted according to the Royal College of Paediatrics and Child Health (RCPCH) recommendations by placing the Pulse Oximeter sensor initially on one foot, obtaining a post-ductal oxygen saturation reading, and then immediately moving the sensor to the right hand to obtain a pre-ductal oxygen saturation reading.[6,7] Then the other two limb saturations were also measured to increase accuracy.

Screening Was Considered Positive If:

1. Oxygen saturation measure is <90% (in the initial screening or in repeat screenings);
2. Oxygen saturation is <95% in the right hand and foot on three measures, each separated by one hour; or
3. >3% absolute difference exists in oxygen saturation between the right hand and foot on three measures, each separated by one hour.

A neonate was categorized as having passed the screening if SaO_2 was more than 95% in all limbs and if the difference in SaO_2 was less than 3%. Screening was performed by specially-trained nurses between 24 – 48 hours of age or at the time of discharge, which is usually after 48 hours. When screening was positive, the neonate underwent a thorough physical examination by a neonatologist and, if indicated, a chest radiograph and an electrocardiogram was done. If no pulmonary condition was found, the neonate was immediately referred for a complete echocardiogram by a pediatric cardiologist, as applicable.

Data Collection and Analysis

The results of screening were entered into the HIS (Hospital Information System) database and stored. For this study we derived descriptive statistics for the number of babies screened, their demographics, the results of the screening, and the associated variables.

Ethics and IRB Approval

The parents or guardians of each child were informed about the screening using a printed brochure prior to the screening. Ethical committee approval for retrospectively analyzing the stored screening data was obtained.

This screening was done between 24 and 48 hours of life. For babies going home on early discharge (discharge before 24 hours), the oximetry was performed prior to

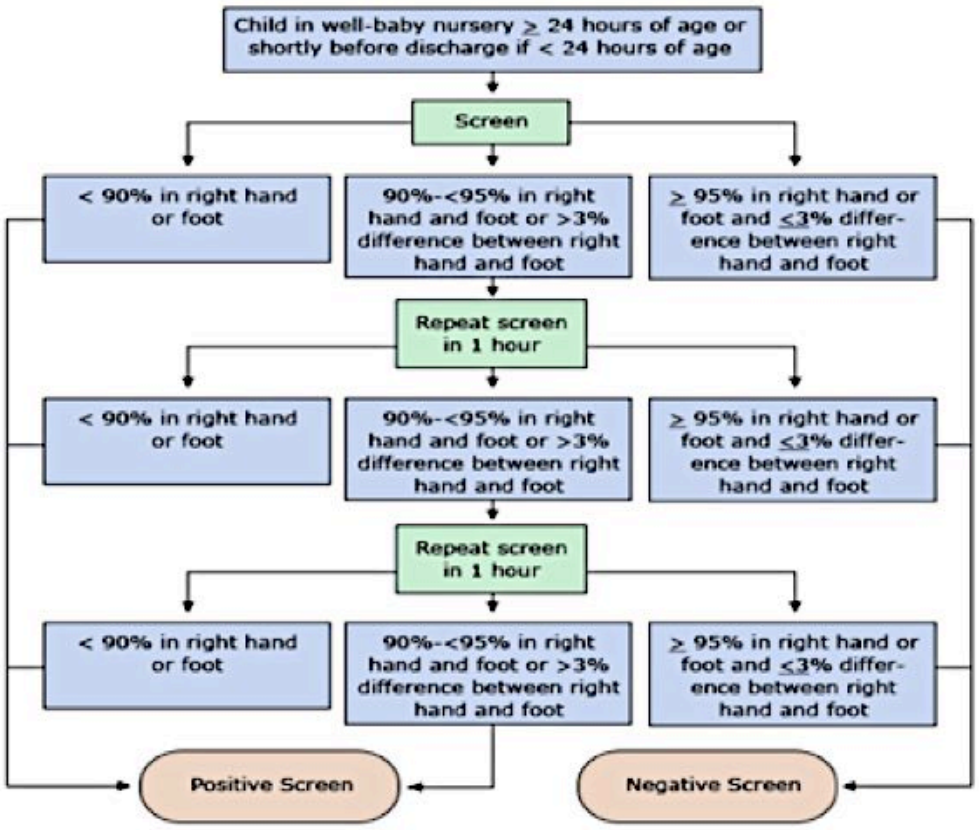

Figure 1. Screening protocol.

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Indication

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Important Safety Information

- INOMAX is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
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INOmax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS

INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOmax. Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOmax therapy immediately.

Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOmax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOmax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOmax and/or FiO_2 should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOmax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

 IMK111-01540 R2 January 2016

discharge and then repeated within the first 3-5 days by the home care team.

A GE saturation monitor with Masimo probe was fixed to the portable trolley of examination equipment, which was used for newborn examination. At the start of the examination, a reusable probe was attached to one foot of the baby with disposable tape (one-inch self-adherent wrap manufactured by 3M); the oximeter was switched on and oxygen saturation documented when the reading stabilized with a strong plethysmographic signal. This typically took between 2 and 4 min. This post-ductal saturation was entered into the hospital clinical records, and also was recorded in the parent-held baby booklet – a personal health record given by the hospital. The probe was cleaned between babies with 70% isopropyl alcohol wipes.

The screening protocol is shown in Figure 1. If the post-ductal saturation was 95% or more, the result was assigned as a pass. Readings between 90% and 95% lead to a repeat saturation measurement in the next 2 to 6 hours. If the post-ductal saturation remained below 95% on repeat testing, the baby was reviewed by a senior neonatologist without waiting for a repeat test.

The hospital electronic, clinical database was searched for all saturation readings performed since commencement of the screening programme. Medical records were searched if further information was needed. Information was collected on the oxygen saturation, the subsequent management, the review by a senior neonatologist, further management and need for echocardiography. We calculated the sensitivity, specificity, positive and negative predictive values, and a false-positive rate.

Results

There were a total of 22,821 babies born after 36 weeks in the study period. Of these, 22,601 babies had saturation screening performed. Of the 220 babies not screened, 207 had been admitted to the nursery and did not qualify for screening, as per our criteria. Screenings were missed in a further 12 babies {not performed because of non-consent by parents (11), performed, but not recorded (1)}. Of the 22,601 babies screened, 22,579 (99.9%) passed the test, and 22 babies (0.1%) were referred. These were babies who had failed the screening protocol, as their initial saturations were difficult to obtain for whatever reason or was <90% or 90-95% on two occasions. Of the 22 cases who were referred, repeat saturation monitoring after a few hours was normal in eight babies, and abnormal in 14 babies. Of the 14 babies with abnormal saturations, an examination by a neonatologist found that three had low saturations secondary to a previously unrecognized pulmonary cause, which was diagnosed following review - these included Persistent Pulmonary Hypertension of the Newborn in one, Transient Tachypnea of Newborn in one, and congenital pneumonia with sepsis in the other.

The other 11 babies who failed oxygen saturation screening underwent a detailed echocardiography by the Paediatric Cardiologist, and one infant had PDA with no other abnormalities, one had a VSD with a small PDA, but no other abnormalities and the remaining nine infants were diagnosed with CCCHD; three were found to have Transposition of Great Vessels (TGV) (3); two were found to have Total Anomalous Pulmonary Venous Drainage (TAPVD) (2); one baby was found to have Tetralogy of Fallot's (TOF); one baby had a VSD, an ASD, and Patent Foramen Ovale with Pulmonary Hypertension; one baby had severe pulmonary hypertension (PAH), and two babies had pulmonary stenosis (PS).

Among these 11 infants, five had been picked up by antenatal scans by our Foetal Medicine specialists in the anomaly scans. All the infants were followed up by the Paediatric Cardiologist and five were referred for emergency cardiac surgery. Three underwent surgery on the 3rd Day of Life (DoL), and are currently alive and thriving. One underwent surgery on Day 7, and is currently doing well. The other underwent surgery on the 9th DoL, but unfortunately, died from post-surgical sepsis.

Analyzing the accuracy of Pulse Oximetry screening in the detection of major CHD, the sensitivity was 89%; specificity was 99.8%; positive predictive value was 0.6% and a negative predictive value was 99.9%. The false positive rate was 0.13%. The routine use of Pulse Oximetry screening in a maternity hospital with over 5,000 deliveries per annum resulted in three extra ultrasounds of structurally normal hearts over the first 52 months.

Discussion

This is the firstPulse Oximetry screening series from India and included 22,601 neonates. Pulse Oximetry screening of healthy newborns provided early alerts to diagnose - life-threatening conditions, both cardiac and respiratory. Successful Pulse Oximetry screening needs appropriate equipment and training. Our study showed similar accuracy to those reported in the recent meta-analysis of 13 studies, which showed a sensitivity of 76.5%, specificity of 99.5% and a low false positive rate of 0.14%.

The 11 cases with major CHD who were identified by Pulse Oximetry were all identified prior to discharge from our service with the clinical alert in all being triggered by the saturation reading, although our foetal medicine experts had picked up five cases antenatally. All 11 cases would probably have been discharged without a diagnosis, had this been in a rural setting without Foetal Medicine specialists. The timely management of these cardiac conditions was vital in optimizing the prognosis for these babies.

We took a pragmatic approach to implementation of the current practice of Pulse Oximetry as one more test in normal newborn examination. The programme did involve employing one extra nurse, and the average procedure time estimated was 8-12 minutes. The main financial costs were the salary for the nurse at Rs. 15,000 per month and the purchase of GE Pulse Oximeters with Masimo probes at an approximate cost of Rs. 50,000 each (though as per new NRP guidelines all maternity hospitals need to have this as part of their NRP guidelines).

The false positive rate was extremely low in our study, which was consistent with the rest of the literature. 'False positive' is really a misnomer in the context of this test. This test is screening for hypoxaemia, which is never normal in a newborn baby. Such hypoxaemia has many causes, just one of which is CHD, and early detection of these other causes can be just as important. Overall, in a published series of 'false positive' cases (e.g. those with low saturations, but a normal heart), about 50% will have some other pathology. The study of Grenelli et al showed a low false positive rate of 0.17%, and that 31/69 'false positives' had other pathology. Our data are consistent with this, as there were three of 14 cases (21%) with low saturations and a normal heart that had previously unrecognised respiratory pathology, some of which was serious, and in which timely management was equally important.

There was just one case of significant CHD identified that was not diagnosed prior to discharge. This was the baby with a large VSD, as this complied with our definition of CHD (need for surgery in the

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first year of life). Parents were upset that this was not diagnosed despite delivering in a tertiary centre and doing all the tests. We identified it as a false-negative case, but saturation screening would not be expected to detect an acyanotic congenital heart lesion at birth. It is a limitation of this study.

In the face of consistent evidence of the benefits of this test, it is reasonable to ask why implementation has been slow in India. The main barriers referred (in informal discussions) in meetings were lack of echocardiography availability, increased workload for Paediatric Cardiology services and paediatric registrars, cost of equipment or concerns about the validity/usefulness of screening and the low rate of positive screens. These barriers are consistent with those described in the 2012 survey of UK practice published by Singh and Ewer.[8] We have looked at these concerns and in the context of our experience have tried to answer them here.

1. **Staffing and Equipment Cost.** This was implemented in our services with the need for one additional nursing staff – but this nurse was also involved in administering BCG vaccine to the babies, and also conducting the hearing test for the newborns. There are relatively minor equipment costs as previously detailed. The total cost to be invested is around Rs. 80,000 per 2 years – and even if it is charged at Rs. 50 per baby (less than $1 per baby) – the cost will be "recovered" with 1,600 deliveries!
2. **Paediatric Cardiology and False Positive Rates.** The main concern is Paediatric Cardiologists' availability and increased burden on echocardiography services. Notwithstanding, most "false positive" have some other significant pathology. The "false positive" rate for CHD in this study, as in the rest of the literature, is extremely low.
3. **Lack of Availability of Echocardiography.** A low saturation screen is not a trigger for an immediate referral for echocardiography. Rather, it should trigger a clinical review by an experienced neonatologist, appropriate investigations and possibly a period of observation. If the clinical pointers are towards CHD and no other cause can be found, then a referral for echocardiography should be requested. At our hospital, we have facilities for Paediatric Cardiology services with less than 4 hours notice. Also, elective referral to a Paediatric Cardiologist is better than a collapsed baby with CCCHD.
4. **Workload:** This was a concern when we first implemented, and for this reason, we incorporated screening into the routine newborn examination and employed one dedicated paediatric nurse to do the test. Once the benefits were seen, there was quick acceptance amongst the staff & obstetricians regarding the value of this test, and this played an important role in promotion of the test.
5. **Cross-Infection Risk:** We adopted a pragmatic approach with re-useable probes and cleaning between patients. The cost is a fraction of what it would be to use disposable probes. There were no cross-infection issues that we are aware of during or since the period of this review.
6. **Discharge Delay:** This has not been a concern in our set-up because the screening was incorporated seamlessly into our baby checks & BCG vaccination after 24-hours. This will clearly vary between services depending on the availability of nursing staff.

The optimal timing of screening remains a controversy. Earlier screening (<24h) results in more false positives, but many of these are important non-cardiac pathology. A late screening results in a lower false positive for CHD and may be more accurate for diagnosis of obstructive left heart lesions, particularly Coarctation of the Aorta. Prudhoe et al showed that Pulse Oximetry is relatively insensitive in detection of coarctation of aorta/interrupted aortic arch (95% Confidence Interval (CI) 24-50%) and TOF (95% CI 24-58%). The AAP recommends screening at 24-48 h. We implemented this as 'late' screening for largely pragmatic reasons. Thus, since 2012, all babies have a saturation measure on the post-natal ward performed by the trained paediatric nurse after 24 hours of birth.

"There is increasing evidence to justify Pulse Oximetry screening as the standard of care.[9,10,11,12,13] As a screening tool, Pulse Oximetry fulfills the requirements. It is inexpensive and easy to use, has a low false-positive rate and allows diagnosis of an important disease process (CCCHD) which has a defined natural history, a suitable confirmatory test, and is treatable. In 2011, the US Health and Human Services Secretary recommended that Pulse Oximetry screening be added to the Recommended Uniform Screening Panel."

There is increasing evidence to justify Pulse Oximetry screening as the standard of care.[9,10,11,12,13] As a screening tool, Pulse Oximetry fulfills the requirements. It is inexpensive and easy to use, has a low false-positive rate and allows diagnosis of an important disease process (CCCHD) which has a defined natural history, a suitable confirmatory test, and is treatable. In 2011, the US Health and Human Services Secretary recommended that Pulse Oximetry screening be added to the Recommended Uniform Screening Panel. In the UK, there remains a wide variation in practice mainly due to a difference in timing of screening. We believe that apart from detecting CCCHD, Pulse Oximetry screening also picks up other important pathology which was previously categorized to be 'false positive'. In our study of the 14 babies with abnormal saturations, 11 had cardiac disease, and the three 'false-positive,' actually had unrecognised pulmonary pathology.

Conclusions

This post-implementation review shows that Pulse Oximetry screening can be introduced into Indian practice with minimal cost and minimal extra burden to echocardiographic services. Our findings mirror those in the rest of the literature with cases of major CCCHD that might have been missed, being diagnosed prior to discharge.[12] The 'false-positive' rate is extremely low, but the term 'false-positive' is a misnomer in this context as over half of these babies had some other pathology. This screening practice should be seen as a test of neonatal well-being, not just for CHD, and should become a standard of care in India, especially now with new IAP NNF NRP guidelines, saturation monitoring at birth has become mandatory; there is no reason why this cannot be done.

For obstetricians this is even more important since they are concerned about the survival of the baby and both mother and baby being normal – this gives extra confidence as one cannot diagnose CCCHD otherwise at birth. This being an inexpensive test and no other new equipment is required, all obstetricians should make it mandatory for their babies to undergo this test which will go a long way to achieve our Millennium Development

Goals (MDG) in reducing our infant mortality and help India achieve the goals.

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Dr. R. Kishore Kumar: conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Arvind Shenoi: Dr. Shenoi carried out the initial analyses, reviewed and revised the manuscript, and approved the final manuscript as submitted. Drs. Kishore Yerur, Prakash Kini and Syed Tajamul were involved in collecting data, and approving the final manuscript. All authors approved the final manuscript as submitted, and agree to be accountable for all aspects of the work.

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Upcoming Medical Meetings

3rd International Neonatology Association Conference (INAC 2017)
Jul. 7-9, 2017; Lyon, France
http://2017.worldneonatology.com/

2017 AAP National Conference & Exhibition
Sep. 15-19, 2017; Chicago, IL USA
https://shop.aap.org/2017-national-conference-exhibition/

Innovations in Neonatal Care
Aug. 7-9, 2017; Austin, TX USA
www.innovationsconference.com

6th National Neonatal Simulation Conference
Sep. 26-27, 2017; Southampton, UK
www.mproveonline.com/conference

7th International Arab Neonatal Care Conference
Sep. 29-Oct. 1, 2017; Dubai Festival City
http://ancc2017.info

8th Phoenix Fetal Cardiology Symposium
Oct. 27-31, 2017; Phoenix, AZ USA
www.fetalcardio.com

20th International Conference on Neonatology and Perinatology
Dec. 4-6, 2017; Madrid, Spain
http://neonatology.conferenceseries.com

Hot Topics in Neonatology
Dec. 10-13, 2017; Washington, DC USA
https://neonatalcareacademy.com/events/hot-topics-in-neonatology/

Specialty Review in Neonatology
Feb. 20 - 25, 2018; Orlando, FL USA
www.specialtyreview.com

NEO: The Conference on Neonatology
Feb. 22-25, 2018; Orlando, FL USA
www.neoconference.com

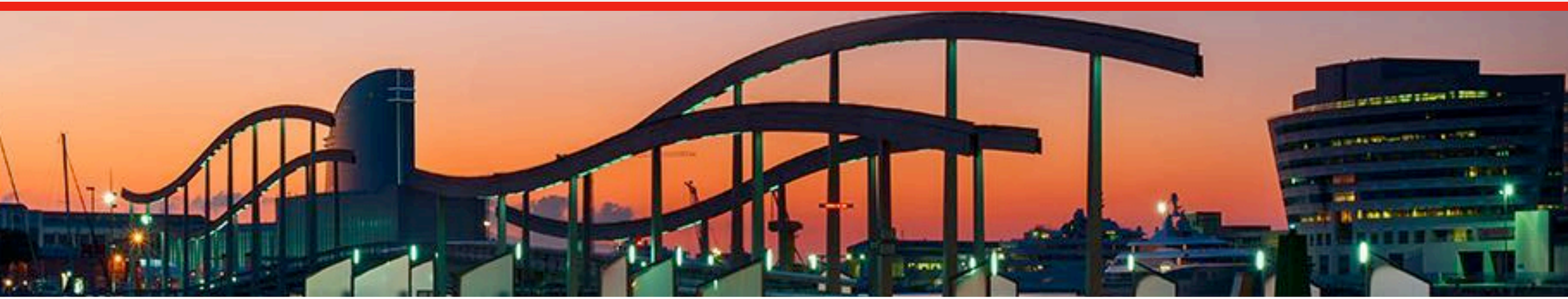
39th Annual NPA Conference
Mar. 14-16, 2018; Loma Linda, CA USA
http://nationalperinatal.org/annualconference2018

Workshop on Neonatal-Perinatal Practice Strategies
Apr. 13-15, 2018; Scottsdale AZ, USA
https://shop.aap.org/2018-workshop-on-neonatal-perinatal-practice-strategies/

16-21 JULY, 2017
7th WORLD CONGRESS OF
PEDIATRIC CARDIOLOGY & CARDIAC SURGERY
Barcelona

www.wcpccs2017.org

WORLD CONGRESS OF PEDIATRIC CARDIOLOGY AND CARDIAC SURGERY



Dear Colleagues,

The Organizing Committee is pleased to announce the **7th World Congress of Pediatric Cardiology and Cardiac Surgery (WCPCCS)**, which will take place on July 16 - 21, 2017, in the Centre Convencions Internacional de Barcelona (CCIB), Barcelona, Spain.
The aim of WCPCCS is to bring together all professionals involved in the care of children's heart disease and congenital heart disease of all ages, from the fetus to the aged. The Congress will provide a unique opportunity to meet the leaders of specialties worldwide; to learn about the latest innovations and the results of procedures; and to contribute to the discussions, debates and plenary sessions with renowned speakers.

The central philosophy of the Congress is "bridging together" all major specialties in the field. Accordingly, the scientific program is carefully planned to address all interests and expertise with concentration streams on pediatric cardiology, pediatric cardiac surgery, adult congenital heart diseases, anesthesia, intensive care and nursing.

We are excited to offer the scientific and cultural feast of a lifetime to one of the most refined crowd in the profession, in one the most welcoming, inimitably exciting venues of the world. Come to Barcelona in July 2017 and join us in forging this unforgettable experience.

Let's meet in Barcelona in July 2017!

Cordial Regards,
Prof. Sertaç Çiçek Congress Chairman, WCPCCS 2017 Prof. Levent Saltık, Congress Co-Chairman, WCPCCS 2017

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Compiled and Reviewed by Tony Carlson, Senior Editor

Two Common Tests Are ineffective in Predicting Premature Births, According to New National Study

Newswise — Two screening tests often used to try to predict which pregnant women are likely to deliver prematurely aren't effective in low-risk women, according to a national collaborative study of more than 10,000 women, led by clinician-researchers at University of Utah Health Sciences and Intermountain Healthcare.

Researchers found that neither transvaginal cervical measurement or fetal fibronectin tests, used separately or together, adequately predicts preterm birth. The findings are published in March 14th issue of the *Journal of the American Medical Association (JAMA).*

Preterm birth, defined as a birth before 37 weeks of pregnancy, is the leading cause of neonatal death or long-term disability. The Centers for Disease Control and Prevention said more than one in 10 births in 2015 were preterm and about 35 percent of infant deaths were related to prematurity. Health-related costs exceed $26 billion each year. A half-million pregnancies ended in preterm birth in 2013, and the preterm rate in the United States lags behind other developed nations.

It has become common to use these screening tests to try to predict expectant mothers who are at high risk for preterm birth, which is hard to predict until it begins. Efforts to stop it once labor has started are largely ineffective, said the study's lead author Sean Esplin, MD, Maternal-Fetal Medicine specialist at Intermountain Medical Center in Salt Lake City and Professor of Obstetrics/Gynecology at the University of Utah School of Medicine.

The cervix is the part of the uterus that's supposed to maintain its thickness and stay hard and closed throughout pregnancy as the fetus develops and puts more pressure on it. Once the pregnancy reaches term and the fetus is ready for life outside the uterus, the cervix softens and dilates. If the cervix thins out and opens too early, a baby is delivered preterm, which may lead to death or long-term complications.

A baby born at 24 weeks, for example, weighs just over a pound and has only a 70% chance of survival. The risk of having a long-term complication related to being born premature is about 50% at that point.

If cervical thinning is spotted soon enough, however, progesterone therapy can be used to intervene and prevent preterm birth. That's led some experts to measure transvaginal cervical length by doing ultrasounds. A length of less than 25 mm is considered short and thus risky.

Because of the human and financial toll of preterm births, some experts have advocated screening all pregnant women that way.

The other test measures fetal fibronectin, an extra-cellular matrix protein that acts like glue between the membrane and uterus lining. As labor and delivery approach, the quantity of fibronectin that leaks from the cervix rises, so swabbing to test vaginal secretions for the protein is sometimes done in hopes of predicting and preventing preterm birth.

To see the effectiveness of those tests — or combining both of them — in predicting preterm birth, researchers at eight clinical centers including, the University of Utah/Intermountain Healthcare, Columbia University, the University of Indiana, Northwestern University, the University of Pennsylvania, Ohio State University, the University of Pittsburgh and the University of California Irvine tested the women at three points during their pregnancies to see whether the results predicted which of them would turn out to deliver prematurely.

The tests were conducted, on average, at around 12 weeks, 19 weeks, and 28 weeks of gestation. All of the women were "nulliparous," meaning they hadn't previously given birth, so there was no history of a preterm birth or identifiable risk factors other than being pregnant. The study didn't include women who'd miscarried before 20 weeks gestation or who terminated a previous pregnancy.

"What we found is that neither of these tests is very accurate," said Esplin. They identify a very small portion of women who are going to have a preterm birth. Of those who have a short cervix, only a portion of them go on to have a preterm delivery."

Because the cervical measurement only identified 8% of women who later had a preterm birth, the researchers said the findings call into question whether the screening should be used routinely. The American College of Obstetricians and Gynecologists doesn't currently recommend that test for low-risk pregnancies.

"This answers a couple of questions," said Esplin. "Transvaginal cervical length and fetal fibronectin measured at different times during pregnancy are poor screening tests for predicting preterm births, alone or in combination. In a low-risk population, if we rely only on these tests to identify women who are highest risk, we're going to miss the vast majority."

"This is a huge trial. This study was our best hope to say how effectively these tests predict the likelihood of preterm birth, and they weren't as effective as we'd hoped," he added.

Now, researchers are looking at other marker combinations to see if they can identify risk factors of adverse pregnancy outcomes, including preterm birth, focusing on protein markers in the blood and social risk factors like age, nutrition and socio-economic factors. They hope to identify early the women at highest risk for preterm birth in order to have time to prevent their preterm births in the future.

Esplin heralded the study as an example of how clinical researchers from Intermountain Healthcare, University of Utah Health Sciences, and others who collaborate to identify interventions that solve problems also increase the cost-effectiveness of healthcare. Preventing preterm birth or prolonging gestation by just weeks would reduce mortality and lifelong complications for babies and save billions of dollars, he said.

"These big multicenter trials are going to give us our best chance to identify women at risk and help them have the best pregnancy outcomes," said Esplin.

The research is part of the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), funded by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

Esplin and Robert M. Silver, MD, are both from Intermountain Healthcare and the University of Utah School of Medicine.

Other study authors are: Michal A. Elovitz, MD, and Samuel Parry, MD, of the University of Pennsylvania; Jay D. Iams, MD, of Ohio State University; Corette B. Parker, MD, and Shannon M. Hunter, MS, of RTI International; Ronald J. Wapner, MD, of Columbia University; William A. Grobman, MD, and Alan M. Peaceman, MD, of Northwestern University; Hyagriv N. Simhan, MD, and Steve N. Caritis, MD, University of Pittsburgh; Deborah A. Wing, MD, and Pathik Wadhwa, MD, University of California at Irvine; David M. Haas, MD, and Tatiana Foroud, PhD, of Indiana University; Matthew K. Hoffman, MD, of Christiana Care; Brian M. Mercer, MD, of Case Western Reserve

University; George R. Saade, MD, of the University of Texas Medical Branch; and Uma M. Reddy, MD, of NICHD.

Vaginal Progesterone Reduces the Rate of Preterm Birth, Neonatal Complications, and Death in Twin Gestations with a Short Cervix

Newswise — Treatment with vaginal progesterone reduced the risk of preterm birth, neonatal complications and death in pregnant women with twins and who have a short cervix— a risk factor for preterm birth— according to a meta-analysis of individual patient data by researchers at the National Institutes of Health (NIH), the Wayne State University School (WSU) of Medicine, the Detroit Medical Center, and other institutions in the United States and abroad.

Births occurring before the 37th week of pregnancy are considered preterm. Preterm birth increases the risk for infant death and long-term disability. Twin pregnancies present a five- to six-times increase risk for preterm birth.

In preparation for birth, the cervix (lower part of the uterus) thins and shortens during pregnancy. In some women, the cervix shortens prematurely, as early as the fourth or fifth month of pregnancy. The natural hormone progesterone (also called the "pregnancy hormone"), inserted in the vagina either as a gel or tablet has been shown to decrease the risk for preterm birth associated with a short cervix in women with a single fetus in previous conducted by NIH and WSU investigators.

The new study, "Vaginal progesterone decreases preterm birth and neonatal morbidity and mortality in women with a twin gestation and a short cervix: an updated meta-analysis of individual patient data," was published in *Ultrasound in Obstetrics and Gynecology.* An accompanying video explaining the study's findings can be viewed at http://www2.med.wayne.edu/prb/progesterone.htm.

"The findings represent persuasive evidence that treatment with vaginal progesterone in women with a short cervix and a twin gestation reduces the frequency of preterm birth, neonatal complications such as Respiratory Distress Syndrome (RDS), and importantly, neonatal death," said the study's first author, Roberto Romero, MD, Chief of the Perinatology Research Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Dr. Romero emphasized that individual patient data meta-analyses represent the "gold standard" in the hierarchy of scientific evidence to answer clinical questions.

"Currently there is no treatment for the prevention of preterm birth in twin gestations," said Sonia Hassan, MD, a co-author of the study. Dr. Hassan is the Associate Dean for Maternal, Perinatal and Child Health at WSU, professor of Obstetrics and Gynecology for the School of Medicine, and director of the Center for Advanced Obstetrical Care and Research for the NIH's Perinatology Research Branch, hosted at Wayne State University and the Detroit Medical Center.

The meta-analysis included the results of six studies, encompassing 303 women pregnant with twins, all of whom had a cervical length of 25 mm or less in the mid-trimester. Of these, 159 women received vaginal progesterone and 144 received a placebo or no treatment. Women who received vaginal progesterone were 31% less likely to deliver before 33 weeks of pregnancy (31% for those who did not). Vaginal progesterone also reduced the rate of preterm delivery before 32 weeks and 34 weeks. All results were statistically significant.

Infants born to patients who received vaginal progesterone had a 30% reduction in the rate of RDS the most common complication of prematurity (from 47% in the placebo/no treatment group, to 33% in the vaginal progesterone group), a 46% reduction in the rate of mechanical ventilation (from 27% in the placebo/no treatment group, to 16% in the vaginal progesterone group), and a 47% reduction in the risk of dying in the neonatal period (from 22% in the placebo/no treatment group, to 11% in the vaginal progesterone group). These results were all statistically significant, as well.

The authors conclude that the results of this individual patient data meta-analysis represents strong evidence that vaginal progesterone in twin gestations with a short cervix reduces preterm birth, neonatal complications and neonatal death. This is the first intervention to successfully reduce both preterm birth and neonatal death.

"One of the most serious complications of multiples in pregnancy is premature birth. In 2014, the Michigan rate of preterm birth due to plurality was over 60%," said Kara Hamilton-McGraw, Maternal Child Health Director for the March of Dimes. "Discovering a successful intervention to address premature birth in multiples could largely impact the rate of babies born too soon and those that, sadly, do not live to see their first birthday."

Founded in 1868, the Wayne State University School of Medicine educates more than 1,000 medical students annually in Midtown Detroit. In addition to undergraduate medical education, the school offers master's degree, PhD and MD-PhD programs in 14 areas of basic science to about 400 students annually.

The Detroit Medical Center (www.dmc.org) operates eight hospitals and institutes, including Children's Hospital of Michigan, Detroit Receiving Hospital, Harper University Hospital, Huron Valley-Sinai Hospital, Hutzel Women's Hospital, Rehabilitation Institute of Michigan, Sinai-Grace Hospital, and DMC Heart Hospital. The Detroit Medical Center is a leading regional health care system with a mission of excellence in clinical care, research and medical education.

Sepsis Risk Prediction Model Decreases Use of Antibiotics in Newborns

Kaiser Permanente, the largest integrated health system in the nation, led the development of a neonatal sepsis risk calculator that has safely reduced antibiotic use by nearly 50% in newborns, according to research published recently in *JAMA Pediatrics.*

Early-onset neonatal sepsis is a systemic bacterial infection that can develop when normal bacteria from the mother's gastrointestinal or genital tract causes an infection in her baby. These infections can be very dangerous in newborns and can result in meningitis or even death.

Since the introduction of routine Group B streptococcus screening and intrapartum antibiotics for at-risk mothers, which is recommended by the Centers for Disease Control and Prevention, the incidence of early-onset sepsis has fallen to less than 0.8 per

1,000 births in 2014. Despite this low incidence, about 15% of babies are still evaluated for infection by blood culture and 5% to 8% receive antibiotics while they are waiting for infection to be ruled out.

"It's often unsettling for new parents to have their newborn's blood drawn or have their babies taken to the Neonatal Intensive Care Unit (NICU) shortly after birth for intravenous antibiotics," said Michael Kuzniewicz, MD, MPH, the study's lead author, a practicing neonatologist and Director of the Perinatal Research Unit at the Kaiser Permanente Division of Research. "We thought there must be a better way to decide which infants were at higher risk, and only evaluate and treat those infants."

The innovative, risk-based approach better targets newborn infants who are at the highest risk for a serious bacterial infection without exposing those at low risk for infection to antibiotics.

Researchers at Kaiser Permanente, the University of Pennsylvania and the University of California, San Francisco, developed a risk prediction model based on data from more than 600,000 babies and their mothers delivered at hospitals in Boston and Kaiser Permanente facilities in Northern California. The result was an online sepsis risk calculator that clinicians can use to help them decide which infants to evaluate and treat for infection. The calculator uses gestational age, time from membrane rupture, maternal temperature and GBS testing results, and use of intrapartum antibiotics to calculate the risk of early-onset sepsis.

In the study, Dr. Kuzniewicz and colleagues compared a baseline period, when care was guided by CDC guidelines (2010 to 2012), to full implementation of the risk calculator at Kaiser Permanente's Northern California birthing centers (June 2014 to December 2015). During the calculator period, in which more than 56,000 infants were born at Kaiser Permanente hospitals in Northern California, blood cultures to evaluate for infection declined 66%, from 14.4% at baseline to 4.9%. Antibiotic use declined 48%, from 5% at baseline to 2.6%.

"An obvious concern with significantly reducing the percentage of infants receiving evaluations for sepsis at birth or empiric antibiotics is missing a baby with a real infection," Dr. Kuzniewicz said. The study found no increase in readmissions for early-onset sepsis or an increase in antibiotics given at 24 to 72 hours after birth, and the rate of early-onset sepsis was unchanged (0.2 to 0.3 per 1,000 births).

"By dramatically reducing the use of antibiotics, the risk calculator allows mothers and babies to stay together in the days after birth," said co-author Allen Fischer, MD, Director of Neonatology for Kaiser Permanente in Northern California. "Instead of admission to the Neonatal Intensive Care Unit for intravenous treatment, the babies remain with their mothers, which improves bonding and the initiation of breastfeeding in the first days of life."

Research has suggested that there may be an association between early exposure to antibiotics and an increased risk of asthma, obesity and autoimmune disorders later in childhood, Dr. Kuzniewicz said. "Antibiotic treatment has risks and benefits, and administration of antibiotics to uninfected infants mean they only assume the risks."

Use of the calculator has begun to expand outside of Kaiser Permanente, with similar results. Co-author Karen M. Puopolo, MD, PhD, neonatologist and Medical Director of Children's Hospital of Philadelphia (or CHOP) Newborn Care at Pennsylvania Hospital, the city's largest perinatal center, said Kaiser Permanente's calculator was implemented as the primary means of newborn sepsis risk assessment in July 2015. "Since that time, antibiotic use has declined by about 50%, and our team is now leading an effort to implement the calculator in all 11 birth hospitals affiliated with CHOP."

Clinicians in 189 countries accessed the calculator about 250,000 times in 2016. Users are primarily located in the United States, but other major users include clinicians in Australia, Canada, the United Kingdom, India, Holland, Chile and Israel.

The study further demonstrates the ways the analysis of big data collected from Kaiser Permanente's electronic health record system, one of the largest private systems in the world, can aid in the development of risk prediction tools that lead to direct improvements in patient care.

"Our work highlights the critical role of implementation strategies and systems, which allow the promise of predictive analytics to be fulfilled," said senior author Gabriel J. Escobar, MD, Regional Director for Hospital Operations Research at the Kaiser Permanente Division of Research.

In addition to Drs. Kuzniewicz, Fischer, Puopolo and Escobar, co-authors were: Eileen Walsh, RN, MPH, Sherian Li, MS, and Patricia Kipnis, PhD, Kaiser Permanente Perinatal Research Unit; and Thomas B. Newman, MD, MPH, University of California, San Francisco, Department of Pediatrics.

The Kaiser Permanente Division of Research conducts, publishes and disseminates epidemiologic and health services research to improve the health and medical care of Kaiser Permanente members and society at large. It seeks to understand the determinants of illness and well-being, and to improve the quality and cost-effectiveness of health care. Currently, DOR's 550-plus staff is working on more than 350 epidemiological and health services research projects. For more information, visit www.dor.kaiser.org or follow them on Twitter @KPDOR.

Kaiser Permanente currently serves more than 11.3 million members in eight states and the District of Columbia. Care for members and patients is focused on their total health and guided by their personal physicians, specialists and team of caregivers. For more information, go to: kp.org/share.

Study Suggests New Way to Prevent Vision Loss in Diabetics and Premature Babies

Researchers at Bascom Palmer Eye Institute, part of the University of Miami Miller School of Medicine, have identified a new molecule that induces the formation of abnormal blood vessels in the eyes of diabetic mice. The study, "Secretogranin III as a disease-associated ligand for antiangiogenic therapy of diabetic retinopathy," which was published March 22nd in *The Journal of Experimental Medicine*, suggests that inhibiting this molecule may prevent similarly aberrant blood vessels from damaging the vision of not only diabetics, but also premature infants.

Changes in the vasculature of diabetes patients can cause long-term complications such as diabetic retinopathy, which affects around 93 million people worldwide. Many of these patients suffer a dramatic loss of vision as the blood vessels supplying the retina become leaky and new, abnormal blood vessels are formed to replace them. A molecule called Vascular Endothelial Growth Factor (VEGF) regulates blood vessel growth and leakiness, and two VEGF inhibitors, ranibizumab (Lucentis) and aflibercept (Eylea), have been

approved to treat retinal vascular leakage, though they are only successful in about a third of patients.

The growth of abnormal new blood vessels also causes Retinopathy of Prematurity (ROP), the most common cause of vision loss in children that affects up to 16,000 premature infants per year in the US. VEGF inhibitors are not approved for use in these patients because VEGF is crucial for vascular development in newborn children.

Study lead-author Wei Li, PhD, Research Associate Professor, and his colleagues at Bascom Palmer developed a technique called "comparative ligandomics" to identify additional molecules that regulate the behavior of blood vessels in diabetic mice. The approach allows the researchers to compare the signaling molecules that selectively bind to the surface of retinal blood vessel cells in diabetic but not healthy animals.

"It is estimated that between one third and one half of all marketed drugs act by binding to cell surface signaling molecules or their receptors," says Li. "Our ligandomics approach can be applied to any type of cell or disease to efficiently identify signaling molecules with pathogenic roles and therapeutic potential."

Using this technique, Li and colleagues discovered that a protein called secretogranin III (Scg3) efficiently binds to the surface of retinal blood vessel cells in diabetic, but not healthy, mice. Though Scg3 promotes the secretion of hormones and other signaling factors, it wasn't thought to have a signaling function itself. Nevertheless, the researchers found that Scg3 increased vascular leakage, and, when administered to mice, it stimulated blood vessel growth in diabetic, but not healthy, animals.

VEGF, in contrast, stimulates blood vessel growth in both diabetic and healthy mice. Li and colleagues think that Scg3 binds to a distinct cell surface receptor that is specifically up-regulated in diabetes.

Treating diabetic mice with Scg3-neutralizing antibodies dramatically reduced the leakiness of their retinal blood vessels. Moreover, the antibodies significantly inhibited the growth of new blood vessels in mice with oxygen-induced retinopathy, a well-established animal model of human ROP.

Though the researchers still need to confirm the role of Scg3 in humans, inhibiting this protein could be an effective treatment for both diabetic retinopathy and ROP, especially as it appears to have no role in normal vascular development. "Scg3 inhibitors may offer advantages such as disease selectivity, high efficacy, and minimal side effects," Li says. "Because they target a distinct signaling pathway, anti-Scg3 therapies could be used in combination with, or as an alternative to, VEGF inhibitors."

LeBlanc et al. 2017. J. Exp. Med. http://jem.rupress.org/cgi/doi/10.1084/jem.20161802?PR.

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