Abstract:

Raydiant Oximetry, Inc. has developed a novel optical-sensing technology (Lumerah™) to directly measure fetal oxygenation during pregnancy through noninvasive, transabdominal fetal pulse oximetry. The clinical use-case envisioned for fetal oximetry is two-fold: 1) assist clinicians in diagnosing fetal hypoxemia during labor and delivery and 2) serve as a tool for 3rd trimester fetal oxygen monitoring to research the etiology of intrauterine growth restriction (IUGR), stillbirth and preterm labor. The clinical and preclinical results of Lumerah are discussed in the following manuscript as well as the history of fetal pulse oximetry.

Introduction:

Pulse oximetry is a noninvasive method of monitoring oxygen saturation of hemoglobin in arterial blood ('oxygen saturation') using a technique of optical plethysmography (measurement of fluctuations in arterial blood volume) and near infrared spectrophotometry (NIRS). Since its introduction into clinical medicine in the 1980s by anesthesiologists for intraoperative care of patients undergoing general anesthesia and patient management in critical care units, pulse oximetry has become ubiquitous in the medical care of neonates, children, and adults throughout the hospital and more widely in general medical practice. Pulse oximetry technology allows healthcare professionals to diagnose and treat dangerously low oxygen levels and has had an enormous beneficial impact on clinical care [1].

Currently, the only patient who does not benefit from noninvasive oxygen saturation monitoring is the fetus. The clinical use-case for fetal oximetry is to assist clinicians in fetal surveillance by providing the ability to diagnose fetal hypoxemia during labor and delivery, improving the accuracy of assessing fetal well-being. There are no commercially available technologies to monitor fetal oxygen saturation in-utero, as the current standard of care for monitoring fetuses during labor is cardiotocography (CTG). CTG monitors the fetus's heartrate and uterine contractions via transducers placed on the maternal abdomen but CTG has serious limitations and poor predictive value in detecting fetal oxygen deprivation during labor [2].

The concept of fetal pulse oximetry is not new. The OxiFirst fetal pulse oximeter was developed in the 1990's by the Nellcor Corporation and was FDA approved in 2001 [3]. The OxiFirst sensor required trans-vaginal/transcervical insertion for placement alongside the fetal cheek; placement required at least 2 cm of cervical dilation, rupture of the amniotic membranes, and fetal descent to at least a -2 station [4].

Nellcor OxiFirst Fetal Pulse Oximeter

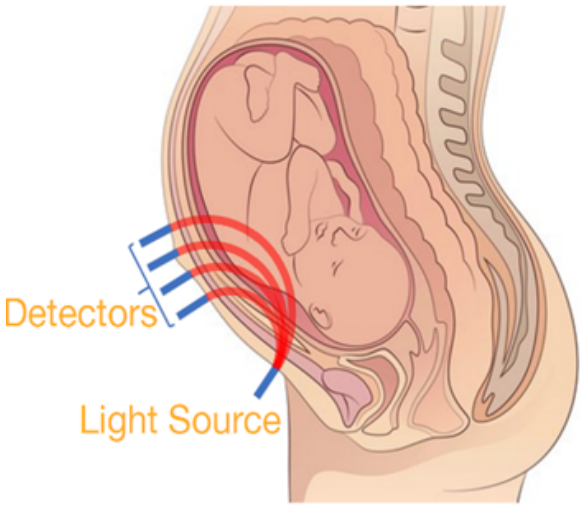
Clinical investigations with fetal pulse oximetry as a research tool demonstrated that the fetus is adequately oxygenated and unlikely to develop metabolic acidosis from hypoxia when oxygen saturation is above 30% [5,6]. When fetal oxygen saturation remained below 30% for at least 10 minutes, metabolic acidosis develops. The development of metabolic acidosis strongly correlates with the development of hypoxic ischemic encephalopathy (HIE) [7].

In three randomized, controlled trials (RCT), the *continuous* use of fetal pulse oximetry resulted in a reduced rate of emergency cesarean deliveries for 'non-reassuring fetal heart rate patterns'; however, it was also associated with an increased rate of cesarean deliveries for dystocia [8,9,10]. Some investigators reported that the continuous use of the Nellcor sensor may have mechanically caused an increased incidence of persistent occiput posterior position which is known to cause dystocia [11,12,13]. When the Nellcor sensor was used *intermittently*, emergency cesarean delivery rates for non-reassuring fetal heart rate patterns decreased but cesarean delivery rates for dystocia **did not increase** [14].

Ultimately a large, multi-centered RCT sponsored by the NICHD did not find that use of fetal oximetry during labor was associated with the primary endpoint of reducing cesarean delivery rates [15]. Although this study had significant design flaws, it was a large study and consequently the American College of Obstetrics and Gynecology (ACOG) did not endorse the routine use of the Nellcor fetal pulse oximeter for clinical practice. The technology was subsequently withdrawn from the market voluntarily.

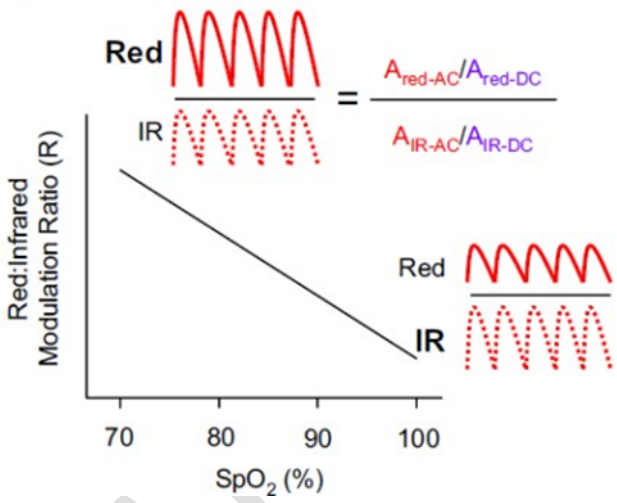
We believe a trans-abdominal form-factor will provide the important information about fetal oxygenation without increasing the incidence of dystocia. In addition, our market research from obstetric providers suggests that fetal oximetry could offer clinical value beyond reducing cesarean delivery rates, such as serving as a tool to standardize and improve communication among the healthcare delivery team when assessing intrapartum fetal status.

Furthermore, transabdominal fetal oximeter has the potential to be used the 3rd trimester before the cervix dilates or amniotic membranes rupture. Use during the 3rd trimester will allow the technology to serve as a research tool to assess fetal oxygen status and develop insights into the etiology of IUGR, stillbirth and preterm labor.



Trans-Abdominal, Near-Infrared Light Propagation for Fetal Oximetry

Theory of Operation:



A Pulse Oximetry Calibration Curve

The theory of operation for pulse oximetry involves propagation of near-infrared (NIR) light into tissue and measurement of the relative changes in light absorption between two NIR wavelengths from a nearby detector to calculate arterial hemoglobin oxygen saturation. Pulse oximetry is based on the principle that deoxygenated-Hb and oxygenated-Hb differentially absorb red and near-infrared light. The ability to target the oxygenation of arterial blood is enabled by the fact that blood from the arterial system pulsates with the cardiac cycle, which is the AC signal. In contrast, blood from the venous system and tissue compartments do not pulsate with the cardiac cycle, representing the DC signal [16].

Transabdominal calculation of fetal oxygen saturation utilizing traditional principles of pulse oximetry requires the measurement of fetal AC and fetal DC signals from the maternal abdomen, and a personalized calibration curve based on the unique maternal/fetal anatomic geometry of that patient. To derive the fetal AC signal, we use a patented methodology for performing a cross-correlation with a fetal heartbeat signal. To derive the fetal DC signal, we developed and patented a methodology using Independent Component Analysis (ICA) to deconvolve the fetal DC from the maternal DC signals.

Intellectual Property:

Our approach to derive the fetal AC signal is covered by US9757058 "Systems, devices, and methods for performing transabdominal fetal oximetry and/or transabdominal fetal pulse oximetry," issued September 12, 2017, and US9986286 "Systems, devices, and methods for performing transabdominal fetal oximetry and/or transabdominal fetal pulse oximetry using a fetal heartbeat signal," issued May 15, 2018. Our approach to derive the fetal DC signal is covered by US11419530 "Systems, devices, and methods for performing transabdominal fetal oximetry and/or transabdominal fetal pulse oximetry using independent component analysis," issued August 23, 2022.

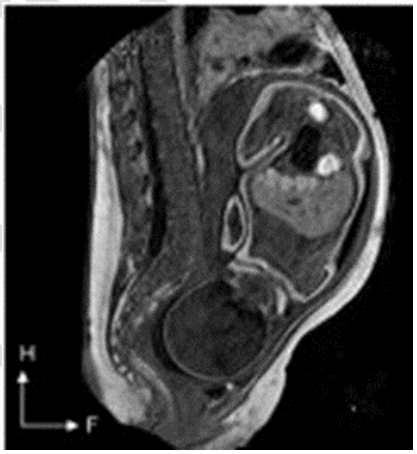
To utilize a personalized calibration curve, our approach is covered by "Systems, devices, and methods for developing a model for use when performing oximetry and/or pulse oximetry and systems, devices, and methods for using a fetal oximetry model to determine a fetal oximetry value". A Notice for Allowance issued on November 08, 2022. Given the foundational IP that Raydiant Oximetry has developed, we believe that any potential competitor attempting to commercialize in this space would have a "freedom to operate" infringement.

Materials and Methods:

Hardware Development

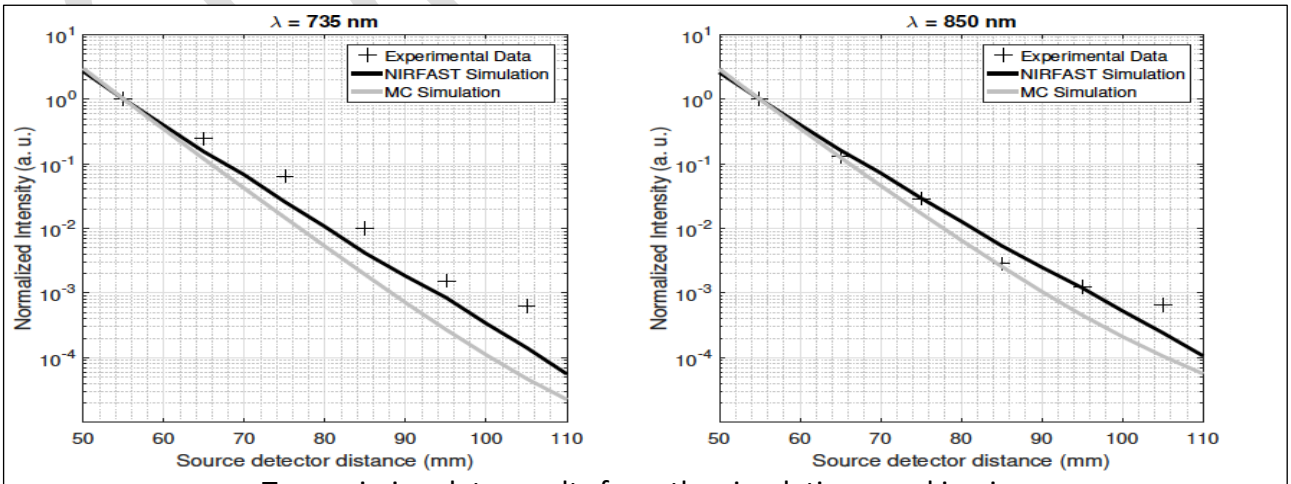
We built a hybrid NIRS system that performs spectroscopic measurements for 16 source-detector combinations ranging from 4 light emitting diodes (LEDs) ranging between 700 and 900 nm and 4 detectors between 2 to 10 cm (Sunrise Labs, Bedford, NH). This instrument was designed to sense a fetus 2-4 cm below the maternal abdominal skin surface. The average fetal depth has been reported to be 2.9 cm with a standard deviation of 0.8 cm [17]. Light power levels used were below the thresholds set for radiance levels by IEC 60601-2-57 and posed minimal risk for thermal injury to the maternal abdomen and optical injury to the fetal retinal tissue.

Algorithm Development



Using MRI and ultrasound images from women in the late 3rd trimester of gestation, we created 7,014 virtual calibration curves to represent "digital twins" of pregnant women and fetus. With the assistance of obstetricians who specialize in ultrasonography, we varied physio-optical parameters and skin pigmentations to develop a comprehensive library of virtual calibration curves.

Subsequently, to validate that these simulated data sets could serve as "digital twins" for in-vivo human data, we initiated an IRB-approved feasibility study of six pregnant women at 36+ weeks gestation, conducted at the UC Davis Medical Center (NCT03013842). We collected human data with a Gen 1 LUMERAH prototype and compared light intensity levels across various source-detector distances and wavelengths of light for maternal AC/DC and fetal AC modulation levels. With additional fine-tuning, the simulated data sets matched the experimental in-vivo human data, allowing us to confidently move forward using these 7,014 virtual calibration curves as the foundation of our algorithm to calculate the fetal oxygen saturation.



Transmission data results from the simulations, and in-vivo measurements from a pregnant woman. (NCT03013842).

We next sought to validate our approach with preclinical data from the pregnant sheep model. Using supervised transfer learning methods, we initiated a process to teach the algorithm how apply simulated data to the in-vivo use case by training the algorithm with labeled in-vivo data.

Animal Study Protocol

The pregnant sheep is considered a robust preclinical model for studying human pregnancy [18]. For studies of transabdominal fetal oximetry, this preclinical model is appropriate given: 1) pregnant ewes with singleton pregnancies can be selected; 2) depth of the fetus from maternal skin in sheep is similar to the depth of fetuses in term pregnant women (2-4 cm); and 3) the oxygen binding properties of fetal sheep hemoglobin are similar to the oxygen binding properties of the human fetus.

We conducted all preclinical experimental animal procedures in accordance with Federal animal welfare regulations and approval of an Institutional Animal Care and Use Committee (IACUC) protocol (BioSurg Labs, Winters, CA). A midline lower abdominal incision was made on time-mated pregnant ewes for uterine exposure. Through a hysterotomy, the fetus was partially exteriorized, and intravascular catheters were placed in fetal femoral arteries bilaterally. One catheter was used for fetal arterial blood sampling and the second catheter was used to transduce fetal arterial pulse (fetal heartbeat signal) in real time to derive the fetal AC optical signal. An inflatable silicone vascular occluder was placed around the umbilical cord to induce graded fetal hypoxia with partial umbilical cord occlusion. Before closure of the hysterotomy, the fetus was fully returned to the uterine cavity and amniotic fluid was replenished with sterile saline solution.

After closure of the maternal abdominal incision, sonography was employed to confirm fetal position and depth from maternal abdominal skin. Baseline maternal and fetal arterial blood gas samples and transabdominal near infrared spectroscopy measurements were obtained with the LUMERAH NIRS system.

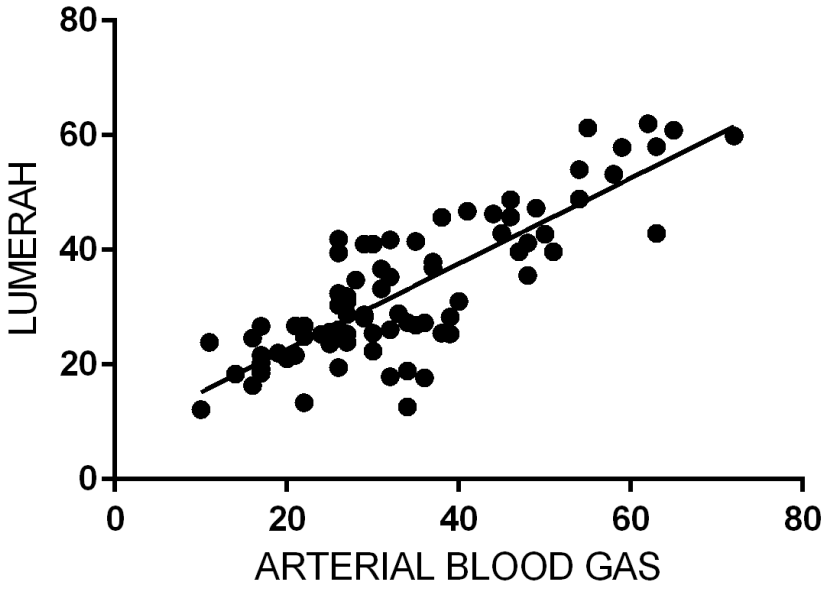
Regression Analysis on Sheep Data:

We collected a total of 261 data sets from 11 pregnant sheep studies that included a ground truth fetal arterial blood oxygen saturation from a surgically placed, fetal femoral artery catheter.

These 261 data sets ranged in fetal oxygen saturation levels from 10% to 70%. We randomly separated the sheep data into two groups: 1) 70% of the data (177 samples) for algorithm training through supervised transfer learning; and 2) 30% of the data (84 samples) as a testing group for algorithm validation.

We defined our accuracy as standard deviation of difference (difference of SaO_2 -SpO_2) and from 84 samples, the SDD was 5.93% with 1 SD (67.5%) of the results within 6.5%. The R^2 was 0.68.

To assess the statistical significance of these correlation results, we calculated the p value using the Pearson's Correlation Coefficient. The results were deemed to be highly correlated as the r(84) = .83, p< .001.



Regression Analysis from Sheep Data (n=84)

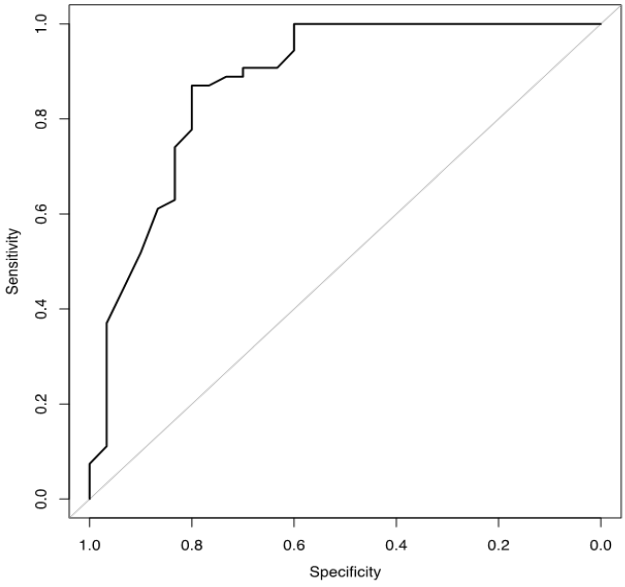
Binary Hypoxia Classifier for Sheep Data:

To establish an initial proof-of-concept for a binary classifier, we choose 35% as the fetal arterial blood oxygen saturation to serve as the cutoff for the fetus at risk for developing acidosis from hypoxia. Prior clinical investigations with fetal pulse oximetry as a research tool demonstrated that when a fetal oxygen saturation is above 30-33%, the fetus is adequately oxygenated and unlikely to develop metabolic acidosis from hypoxia.

When we binarized the 84 sheep samples, the results yielded a sensitivity of 89% and a specificity of 81% with an AUC of 0.88. If we targeted the highest possible sensitivity to mitigate for false negatives, we could achieve a sensitivity of 99% and a specificity of 60%.

If we subjected the 84 data samples to an a-priori signal quality metric, we could improve the sensitivity to 99% and the specificity to 95% but expect that 20% of the sheep results would not report a value.

These results confirmed that our approach to solving transabdominal fetal pulse oximetry were working and allowed us to move forward with a feasibility study of women and their fetuses in labor to clinically validate our approach.



ROC Curve for Binary Hypoxia Preclinical Classifier

Human Study Protocol

Through an IRB approval feasibility study on 30 laboring women at the University of Texas Medical Branch (UTMB) in Galveston, Texas, we consented 31 patients and collected Lumerah data on 23 laboring women (NCT05147584). A key difference between the human study protocol and the animal protocol was that the ground truth for fetal human oximetry measurement was with a Nellcor OxiFirst sensor while the ground truth in the ovine experiments was arterial blood gas measurements.

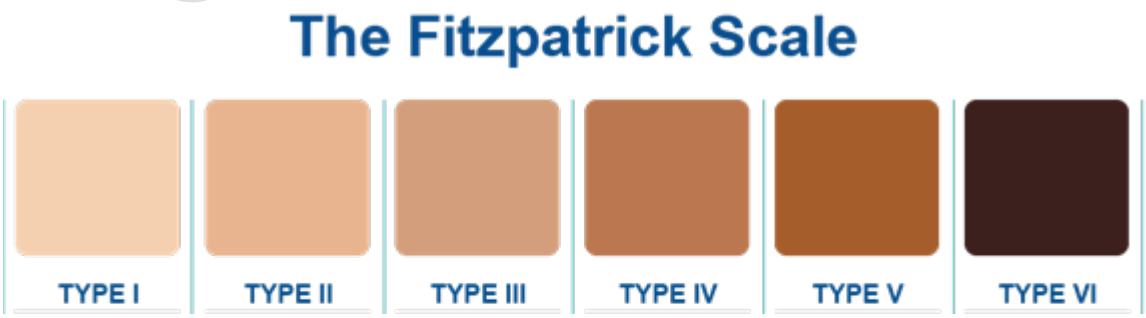
The clinical study was initiated on July 18, 2022 and completed on December 15, 2022. We choose to work with UTMB in Galveston, Texas because the site is part of the NIH MFMU research collaboration, and the PI was Dr. George Saade – the editor-in-chief for the American Journal of Perinatology.

120 patients were screened, and 31 patients consented to participate in the study. The key reasons for screen failures included: 1) fetuses under 37 weeks gestation; 2) maternal infection such as COVID, HSV or Group B Strep; and 3) mother was under the age of 18 or above the age of 40.

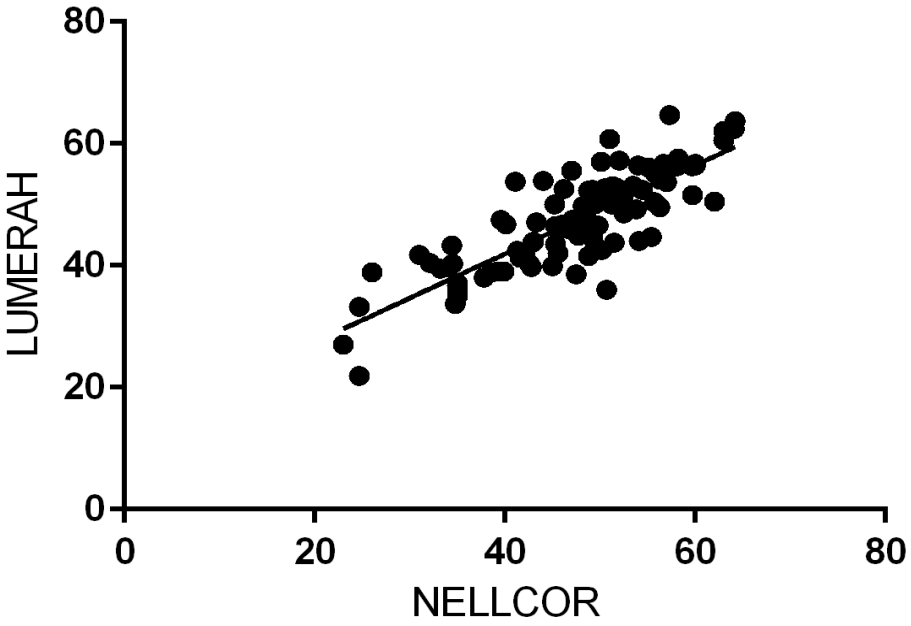
Of the 31 participants who consented, 23 patients were enrolled, and we were able to initiate and complete data collection on 16 patients. From the 16 patients, > 50% had skin colors of Type 3+ skin pigmentation based on the Fitzpatrick Scale.

Overview of Human Data

From the 16 laboring women, we collected 102 data pairs that ranged in fSpO2 levels from 23% to 64%. The mean fetal oxygen saturation in our data set was 47.0% with 1 SD of results +/- 9.3% and 3.9% of the results below 30%. In a cohort of 118 patients, East et al. reported that the mean fetal oxygen saturation was 46.9% with 1 SD of results +/- 9.1%, and 3.9% of the results below 30% [19]. This gave us the confidence that although our sample size represented only 16 patients, it was highly representative of the general population.



Regression Analysis on Human Data:



Regression Analysis from Human Data (n=102)

From the 16 laboring women, we collected 102 data pairs that ranged in fetal oxygen saturation levels from 23% to 64%. To train and validate the algorithm, we used a technique called "leave-one-out cross validation." With this approach, one trains the algorithm with 101 data pairs and then validates on the final data pair, repeating this cycle until all 102 data pairs are assessed.

The mean average error for the human data set was 3.78% and the root mean square error 5.16%. The R^2 was 0.68.

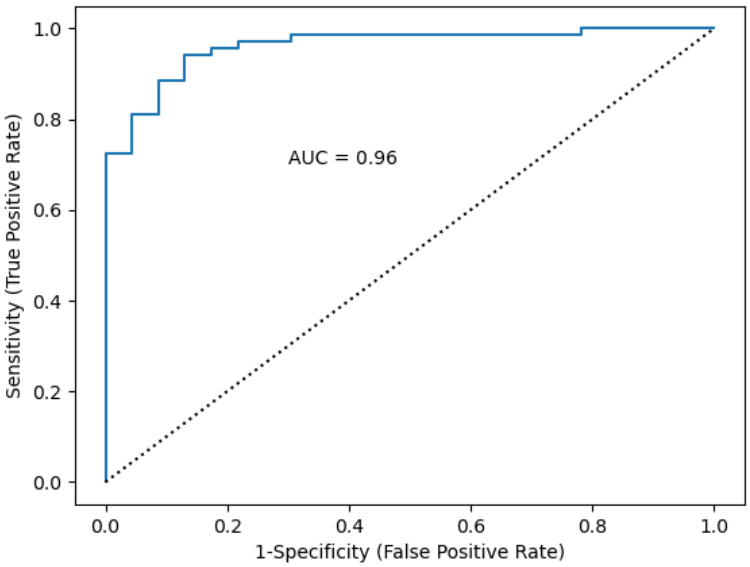
When we assessed the performance for various skin pigmentations, we had a mean average error for the human data set was 3.75% and the root mean square error 5.13% for type I-III skin colors. For type IV-VI skin colors, we had a mean average error for the human data set was 3.97% and the root mean square error 5.34%.

To assess the statistical significance of these correlation results, we calculated the p value using the Pearson's Correlation Coefficient. The results were deemed to be highly correlated as the $r(100) = .83$, $p < .001$.

Binary Hypoxia Classifier for Human Data:

To establish an initial proof-of-concept for a binary classifier, we choose 35% as the Nellcor OxiFirst fetal oxygen saturation to serve as the cutoff for the fetus to be at risk for developing metabolic acidosis from hypoxia.

When we targeted the best combination of sensitivity and specificity, we achieved a sensitivity of 95% [95% CI 72.7% to 99.9%] and a specificity of 84% [95% CI



ROC Curve for Binary Hypoxia Clinical Classifier

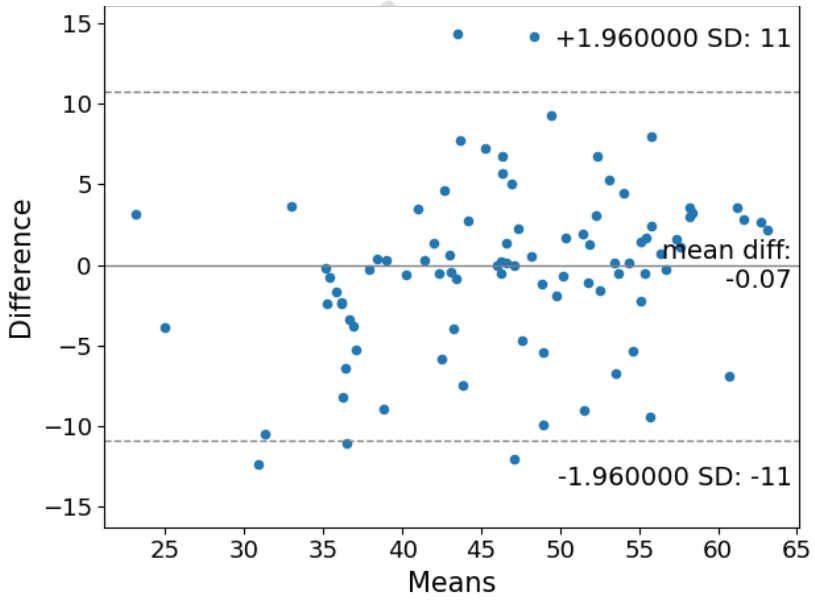
77.5% to 93.2%] with a Youden's Index of 81.2%. The AUC for the ROC curve was 0.96. When we target the highest possible sensitivity to mitigate against false negatives, we could achieve a sensitivity of 100% [95% CI 81.5% to 100%] and a specificity of 81% [95% CI 70.6% to 88.6%] with a Youden's Index of 80.7%.

To assess the statistical significance of the sensitivity/specificity results, the p value was calculated, using Fisher's Exact Test for a 2X2 table. The p value was < .001 and the resulted deemed statistically significant.

Limits of Agreement for Human Data:

In the guidance document for premarket notification submissions of pulse oximeters, the FDA recommends submitting a Bland-Altman plot with the root mean square error and upper & lower 95% limits of agreement from at least 10 subjects and 200 data points [20].

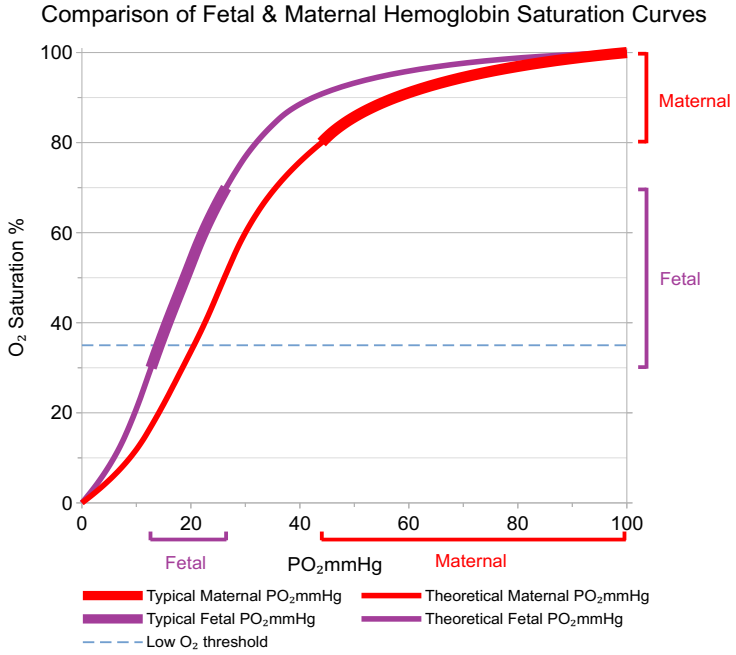
The RMSE was 6.7% with the 95% upper LoA was 11.2 while the 95% lower LoA was -11.



Bland-Altman Plot for Limits of Agreement

Discussion:

Fetal hemoglobin has evolved with stronger oxygen binding properties than adult hemoglobin [21]. A change of 10 mmHg in PO2 for fetal hemoglobin will result in a 30% change of oxygen saturation in-utero while a change of 10 mmHg in PO2 for adult hemoglobin will result in a 5% change of oxygen saturation. These larger variations seen with fetal hemoglobin are a result from the fetus living on the steep-portion of the hemoglobin disassociation curve and translates into larger Standard Deviation of Differences (SaO_2-SpO_2) to be expected from fetal pulse oximeters compared to traditional adult/pediatric pulse oximeters [20].



Comparison of Adult vs Fetal Hemoglobin Saturation Curves

The fetus in-utero lives with an oxygen saturation around 50% while healthy adults and children breathing room air live at an oxygen saturation above 95%. Given the limitations of oxygen transport across the placenta, a fetus in-utero cannot have an oxygen saturation above 70%. For CTG monitoring the reported fetal heart rate can erroneously be the maternal heart rate, and although the maternal heart rate is usually much lower than the fetus, they can overlap. For the fetal oximetry application, it is unlikely that a transabdominal fetal oximeter would report the maternal oxygen saturation because the values are vastly different, and an external pulse oximeter can be used to confirm the maternal arterial blood oxygen saturation.

A key difference in our animal study protocol from the protocol from other academic investigators that studied transabdominal fetal pulse is that the other groups partially return the fetus into the uterine cavity and left the head of the fetus out of the uterus and below the maternal abdominal wall [22,23,24]. An additional key difference is the methodology for inducing fetal hypoxia. The academic groups inserted a catheter with an inflatable balloon into the maternal aorta from the maternal femoral artery in order to directly reduce blood flow to the uterus and subsequently the fetus. However, this approach also desaturates the lower extremity of the mother as well as the maternal uterine wall and confounds the desaturation results from the fetus.

We believe that our results represent a stronger technology validation because we would fully return the fetus into uterine cavity. Furthermore, utilizing an occluder around the umbilical cord to create fetal hypoxia is more representative of the pathophysiology experienced during human pregnancy and our results are not confounded by the simultaneous desaturation of maternal/uterine tissue.

In addition, our clinical study results demonstrate feasibility that is above and beyond what others have published to date. While other groups have demonstrated that they can detect a transabdominal human fetal AC signal, none have been able to validate that they can calculate the fetal oxygen saturation with clinical grade accuracy [25].

We believe that the preclinical and clinical results presented offer a compelling proof of concept that transabdominal fetal oximetry is feasible in laboring women, and that this technology will confer tremendous clinical benefit to all relevant healthcare stakeholders.

To better understand the context of our preclinical results, we reviewed the preclinical accuracy specifications of the Nellcor OxiFirst Fetal Pulse Oximeter submitted to the FDA in 2000. An independent laboratory completed a verification study on 4 piglets and obtained 247 data pairs. They gathered arterial blood oxygen saturations that ranged between 6% to 100% and reported a Standard Deviation of Difference (SaO_2-SpO_2) of 5.3% with 1 SD (67.5%) of all results within 6% [26].

These fetal oxygen saturation measurements were obtained from the fetal sensor that was placed directly on the piglet.

Subsequently, to validate that the piglet calibration was appropriate for human use, the Nellcor OxiFirst fetal pulse oximeter was utilized on neonates and infants with cyanotic congenital heart defects and/or severe pulmonary dysfunction. From 27 babies, 72 data pairs were obtained with fetal arterial oxygen saturation ranging from 34% to 95%. The Standard Deviation of Difference (SaO_2-SpO_2) was 5.4% and the FDA deemed that the calibration performed on animals to develop the Nellcor OxiFirst system was appropriate for use on humans and the Nellcor fetal oximeter was approved by the FDA in 2001 [27].

The potential clinical utility of transabdominal fetal oximetry over CTG technology is compelling. CTG has been reported to have a sensitivity of 85%-93% and a specificity of 29-40% for the detection of 'fetal distress' [28]. The low specificity of CTG technology leads to increased rates of false positives with the clinical consequence of the overuse of emergency cesarean deliveries for suspicious 'non-reassuring fetal heart rate patterns [29]. The initial results from the binary hypoxia classifier suggests that transabdominal fetal pulse oximetry combined with CTG technology could significantly improve the specificity for the detection of 'fetal distress' and reduce false positives associated with Category II fetal heart rate patterns [30]. Lumerah's sensitivity and specificity results have been consistent with the results from Nellcor, where a sensitivity from 93%-100% and a specificity of 81% -87.4% was reported for the detection of newborn metabolic acidosis [6,31].

In addition, Clark et al. published in 2017 that in a cohort of 120 fetuses born with metabolic acidosis, 65/120 of fetuses had fetal heart rate tracings that did not suggest fetal distress [32]. Graham published in 2014 that of the 39 babies born with hypoxic ischemic encephalopathy, 4/39 fetuses had normal category I tracings prior to birth [33]. We believe that Lumerah's increased sensitivity for detecting fetal distress could lead to an improvement in the identification of the newborn at risk for developing metabolic acidosis and hypoxic ischemic encephalopathy.

Given that Lumerah has preclinically and clinically demonstrated similar accuracy specifications, sensitivity, and specificity to the results reported for Nellcor, we hypothesize that similar accuracy, sensitivity, and specificity will follow for Lumerah from the pivotal study for FDA clearance. Furthermore, with a diagnostic tool that has similar performance to the Nellcor system, we also hypothesize that Lumerah will reduce emergency C-section rates by 50% for suspected fetal distress, as was previously reported in 4 RCT studies with the Nellcor fetal oximeter, but without increasing C-section rates for dystocia [8,9,10,14]. Such results could potentially position Lumerah to become the standard of care for fetal monitoring across the globe.

Conclusion:

Stakeholders in obstetrics continue to hope that the "original promise of fetal pulse oximetry would one day be fulfilled with instrumentation refinements" to the original Nellcor OxiFirst design [12]. We believe that these preclinical and clinical results offer the strongest proof-of-concept for transabdominal fetal pulse oximetry published to date. Our next steps will be to present these results to the FDA to finalize the pivotal study design and data development plan.

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