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Review Article

Review of Optical Methods for Fetal Monitoring in Utero

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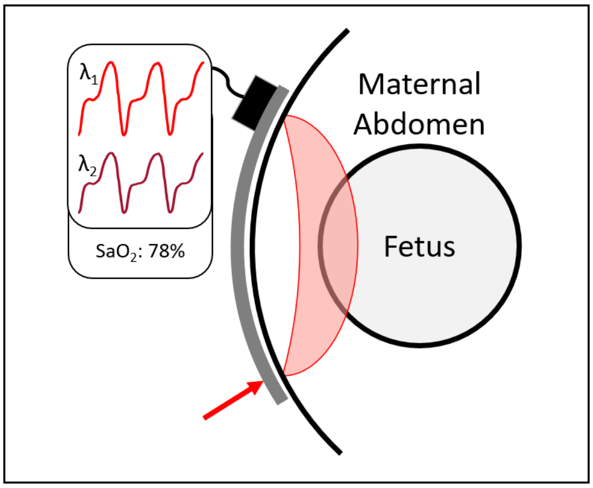

The current technology for monitoring fetal wellbeing during child birth is cardiotocography. However, CTG has high false positive rates that lead to unnecessary emergency Cesarean deliveries and false negatives that result in birth injuries. To curtail these issues, fetal pulse oximetery has been a topic of interest for many decades. Fetal pulse oximetry would yield the oxygen saturation of the fetus in utero and provide a more robust marker for clinicians to make decisions about performing emergency Cesarean deliveries. Here we present a review of biomedical optical developments related to transabdominal fetal pulse oximetery in the biophotonics field and the challenges that must be overcome to make transabdominal pulse oximetry a clinical reality.

KEYWORDS

Pulse oximetry, fetal monitoring, light propagation modelling, phantom studies, pre-clinical studies, clinical studies

1 | INTRODUCTION

In 2019 there were 3.7 million births in the United States, 31.7% of which were by Caesarean (C) delivery [1]. The standard of care for monitoring fetal wellbeing during labor is cardiotocography (CTG), which uses Doppler ultrasound to monitor fetal heart rate and a pressure transducer to monitor maternal uterine contractions. Continuous CTG (electronic fetal monitoring) has been shown to reduce neonatal seizures, but leads to an increase in C-deliveries [2, 3]. One study evaluated CTG fetal heart rate (FHR) patterns by their baseline, decelerations, variability, as well as accelerations and compared these to fetal scalp pH measurements. They were able to demonstrate a sensitivity of 95% for suspect of pathological samples but a specificity of 21.8% for fetal acidosis [3]. Another study used FHR patterns to determine fetal acidemia in which they had a sensitivity of 63% and a false-positive rate of 89% [4]. A third study looked at patterns of FHR variables to determine fetal asphyxia during labor, but only had a sensitivity of 17% and a positive predictive value

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between 18.1% to 2.6% [5]. Additionally, the use of the CTG has caused an increase in Caesarean deliveries with no difference in outcomes for cerebral palsy, infant mortality or metrics of fetal wellbeing [2, 3]. Currently, the ability to detect fetal metabolic acidemia during labor and reduce C-deliveries depends on the advancement of technology [6, 7]. Therefore, there is a direct clinical need to develop devices that directly measure fetal oxygenation and the hemodynamics of the fetus. Near infrared diffuse optical spectroscopy has the potential to provide non-invasive monitoring of oxygen content of a fetus *in utero* [8].

Transvaginal pulse oximetery was one solution that has been proposed in the past. The transvaginal pulse oximeter

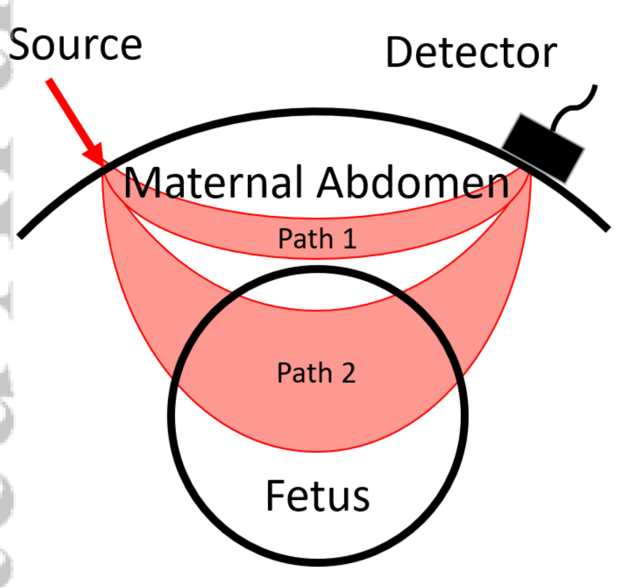

FIGURE 1 Example of typical setup of transabdominal pulse oximetry. There is a source that emits light into the mother's abdomen and it can travel two different paths. Path 1: The light only travels through the mother and then is detected. Path 2: The light travels through the mother, to the fetus, and through the mother again to be detected. This results in a mixed signal containing both mother and fetal components.

was placed directly on the fetus' cheek during labor. Although a large trial showed that fetal pulse oximetry did not reduce the rate of C-delivery [9], a recent review discussed that this may have been due to lack of protocol compliance in the clinical study. The transvaginal pulse oximeter may also have a risk of infection, interfering with the progress of labor, or slipping off the cheek of the fetus [10]. Due to these complications, transabdominal pulse oximetry has been proposed as a more non-invasive means of determining fetal oxygenation. The FDA approved a transvaginal pulse oximeter in 2000 [11], but it was not widely adopted and subsequently removed from the market. Although transvaginal pulse oximetry is an invasive test, transabdominal pulse oximetry is completely noninvasive and has the potential to be integrated into existing labor monitoring systems (e.g. CTG) to provide clinicians an additional metric about fetal wellbeing.

Thus, transabdominal pulse oximetry has been proposed as a solution to measure fetal arterial oxygen saturation. The basis behind this technique is that there is a light source placed on the abdomen of the mother. The light travels through the mother's tissue, reaches the fetus, and then travels back to the surface of the mother where the light can be detected (See Figure 1). The light that is detected has a combination of maternal and fetal contributions to the signal.

Transabdominal fetal pulse oximetry has been an area of interest since the 2000s when Britton Chance's group published several studies [8, 12-18]. There are many different approaches taken to determine the feasibility of fetal pulse oximetry. Computational modelling in the literature was used to determine design parameters and efficacy of detection. There were also phantom studies to test prototypes. Last, pre-clinical and clinical studies were performed to determine overall feasibility within the realistic conditions that transabdominal fetal pulse oximetry might encounter.

2 | Traditional Pulse Oximetry

Pulse oximetry is used to continuously and non-invasively monitor arterial oxygen saturation (SaO_2), usually to assess respiratory function (See FIGURE 2A for example of an at home pulse oximeter) [19]. The technique works by utilizing two wavelengths of light in the red and near-infrared range to extract the content of two chromophores in the tissue. Oxy-hemoglobin and deoxy-hemoglobin absorb the red and near-infrared light differently, providing the contrast necessary to determine oxygen saturation. A pulse oximeter records a photoplethysmogram (PPG), which is an optical signal measured over time to obtain the patient's pulse, or the dilation/relaxation of the arterial blood vessels (See FIGURE 2B). The measured optical signal contains a non-pulsatile part or "direct current" (DC) and a pulsatile component or "alternating current" (AC) [19]. In pulse oximetry, we are interested to find the oxygen saturation of the blood in the arteries changing volume during the heart pulse, meaning blood saturation in the pulsatile signal.

To find the oxygen saturation, the ratio of the measurement of the two wavelengths must be determined. The ratio (R) is calculated using the following equation:

$$R = \frac{AC^{\lambda_1}}{DC^{\lambda_1}} \Big/ \frac{AC^{\lambda_2}}{DC^{\lambda_2}}. \quad (1)$$

where the AC value is the difference between the maximum and minimum values of the PPG signal, while the DC value is the minimum value of the PPG signal, λ_1 and λ_2 are the two wavelengths used for the pulse oximetry device. The ratio is then compared to previously obtain empirical data from healthy volunteers whose oxygen saturation was altered between 100% and 70%. The data from the healthy volunteers is then used to find a calibration curve. Then, the curve is used to determine the oxygen saturation by using a newly measured R (See FIGURE 2C).

This traditional method of pulse oximetry cannot be utilized for transabdominal pulse oximetry. The DC component of Eq. 1 has both maternal and fetal influences. In order to obtain the ratio for the fetal pulse the DC component of the fetus without the mother would be needed [12].

3 | Computer Modelling

3.1 | Monte Carlo

Zourabian et al. ran Monte Carlo simulations to demonstrate "the optical shunt problem" of trans-abdominal fetal oximetry, where some of the light is going between the source and detector through the maternal tissue only without passing through the fetus [12]. To measure the signal from the fetus, the light needs to travel through the mother, to the fetus, and back through the mother to the surface for detection. The signal will consist of pulsations caused by both the maternal and fetal heartbeats. The frequencies of these two pulses can be easily separated with a Fourier transform. However, obtaining the oxygen saturation is much more difficult and requires the normalization of the modulated signal by the DC signal yielding the light attenuation passing through the tissue, both through the maternal and fetal tissues. Two possible solutions are to assume a value for the maternal DC levels or to neglect the mother's contribution to the DC light levels. Through the simulations and neglecting the mother's contribution to the DC levels and modulating the fetal optical properties by 5%, Zourabian et al concluded that the error in absolute measurements could be very high, however, if a ratio is taken of two wavelengths, then the error could be acceptable. Additionally, they saw that the fraction of light contributed from the fetal layer increased as source-detector distance increased. This model, however, is unrealistic for near-term pregnancies since the maternal layer and amniotic fluid layer were each 1 cm in width in the simulations.

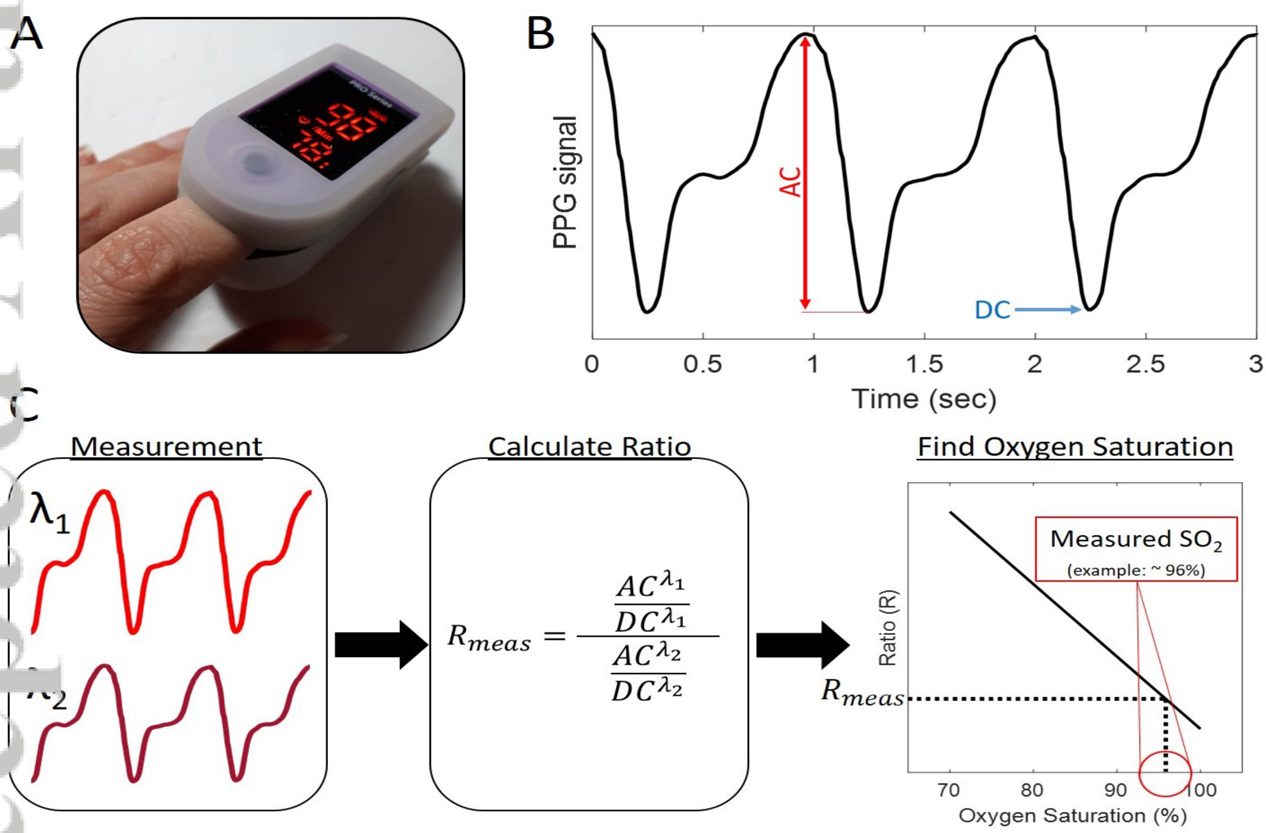

FIGURE 2 An example of a commercial pulse oximeter taking a reading (A). An example of a PPG signal that is captured by the pulse oximeter to be processed. The AC parameter is the difference between the maximum and minimum of the PPG signal, while the DC parameter is the minimum value (B). A flowchart of how the oxygen saturation is determined (C). The measurement is taken at two different wavelengths of light. The ratio (R_{meas}) is calculated using Eq. 1. Then using empirical data previously determined on a set of healthy volunteers, the ratio is compared to the previous data and the oxygen saturation is determined.

Monte Carlo was also used to determine source-detector configuration using a software called TracePro [20]. A three-layer model was created using similar optical properties as another study [15]. Simulations were run for fetal depths of 2.5 cm, 3.7 cm, and 4.9 cm. However, only the 2.5 cm model was analyzed, since the authors suggest that, in the other cases, the losses are so high that the light that had reached the fetal layer could not be detected. Yet, this is more likely due to only 2 million photon packages were used to run the simulation. Two million packages would not be enough to accurately predict the output power centimeters away from the source. A source-detector distance of 4 cm was chosen based on the capabilities of the silicon photodetector and adaptive filtering techniques of their system. This also allowed for 70% of the optical power to come from the fetal layer given that the fetus was 2.5 cm below the surface of the mother while retaining 10^{-6}-10^{-10} W/cm^2 of optical power. This study also shows the balancing act needed between the output optical power and the portion of the signal that comes from the fetus, which can be solved by using the proper source-detector distance. Also, this study observed the amount of light that can travel through the tissues not the dynamic signals that come from a pulse.

Another Monte Carlo study was conducted in which the algorithm was modified to allow for a layered spherical geometry [21]. The goal was to observe the static signal (not the dynamic pulse signal) at different source-detector locations for different fetal depths and radii of the mother's abdomen. The conclusion was that proper source-detector configuration and positioning was necessary for individual cases in order to achieve a proper signal. As the fetal depth increased the optimal source-detector distance for measurements also increased. For example at a fetal depth of 2.5 cm the maximum ratio of the mixed component of the signal (fetal plus mother) to the total signal would be for a source detector distance around 8 cm. While at a fetal depth of 5.5 cm, the source-detector distance would be around 15 cm. Additionally, by increasing the radius of the maternal abdomen an increase of the percentage of mixed signal to the overall signal was observed with optimal source-detector distances between 8-11 cm. However, since the fetal depth was kept constant, to our understanding, the fetal layer would have had to increase in size to compensate for the increase in the radius of the maternal abdomen. This could have contributed to the increase in mixed signal since there would have been a greater fetal volume. Yet, this would not be a realistic understanding of the size of the fetal head, which would not have a radius of 27.5 cm (30 cm radius – 2.5 cm mother layers). Continuing with the simulations, the planar and spherical geometries were compared [22]. When comparing the fluence at the surface, the two models are similar with the spherical model giving slightly higher fluence measurements. When looking at the ratio of the mixed component with the total signal the plane model has sigmoidal shape leveling off at 12 cm (~60%), while the spherical model has a peak around 8 cm (~50%). Such models are important to determine the source-detector configuration of a potential system. Spherical geometry showed different results from the planar geometry that must be taken into consideration when designing transabdominal pulse oximeters.

One group used Monte Carlo simulations to determine the influence of dilation of the blood vessels and number of photons that can be detected [23]. There was a decrease in photons (~1% of photons) when the mother blood vessels went from diastolic to systolic, but there was little change (<<1% of total photons) when the fetus varied from one state to the next. The small resulting signal modulation must be taken into account during system design to have sufficient resolution and dynamic range. While the previous studies focused on optical outputs, this one focused on the changes in optical output caused by the heartbeat. However, the pulsatile signal is necessary to establish SaO_2 in which the authors demonstrate how the signal is much smaller than the mother signal. Therefore, transabdominal pulse oximetry must be sensitive to these small optical changes.

MC simulations were also used to determine the effect of amniotic fluid on the output measurements of a transabdominal optical system (static light measurements) [24]. Since amniotic fluid is fairly translucent (low scattering), the diffusion approximation cannot be used to estimate how light propagates through the medium. However, the amniotic fluid layer is thin when mother nears the end of the pregnancy. The MC simulations showed distinct differences between the measurements with the models with amniotic fluid (1 mm thick layer) compared to those without. For example, with a fetal depth of 20 mm, a source-detector distance of 9.5 cm and a 735 nm wavelength there was nearly a 2 magnitude difference in the intensity on the detector between the two models. The study showed the importance of considering amniotic fluid in the models, which is occasionally neglected in diffusion models due to its low scattering nature or because it is a small layer. The small amniotic fluid layer Is often justified by near-term pregnancies in which the head of the fetus is close to the mother's abdominal layers.

3.2 | Finite Element Methods

Böttrich et al. used COMSOL Multiphysics to create a 5-layer tissue model in which the diameter of the arteries were modulated in order to simulate a heartbeat [25]. A comb filter was used to separate the maternal and fetal signals. The comb filter was used in order to suppress the harmonics of the maternal heart beat as well as the primary signal. In additional work, they extended the method by including an adaptive noise canceller [26] and used further processing to extract the mean shape of the fetal pulse wave by using synchronous averaging of several detected pulses [27].

Using diffusion theory, a two-layer spherical model was used to understand the effects of the fetus's head on the signal [18]. The scattering coefficient was kept the same for both layers (μ_s' = 4 cm^{-1}) while the fetal layer had a μ_a = 0.125 cm^{-1} and the mother μ_a = 0.08 cm^{-1}. With the fetus 2.5 cm under the surface of the mother, there was a 10% decrease in measurement for a 6 cm source-detector separation and a 53% decrease at the 10 cm source-detector separation when the fetus is present compared to when the fetus is not present (maternal tissue only). The transport factor (normalized fluence rate) was calculated for the mother with and without the fetus. At small source-detector distances these two factors are very similar and could be used to extrapolate the expected transport factor of the mother only at larger source detector distances [18]. The fetus is more absorbing than the mother and therefore contributes to a greater loss in signal compared to when there is no fetus present, which poses another challenge to transabdominal pulse oximetry.

3.3 | Computational Modelling Summary

The computational modelling of both static (no pulse) and dynamic (pulse) fetal signal is very important to the design process of transabdominal pulse oximetry. The static studies can approximate the amount light that can reach the fetus in highly scattering medium when it is centimeters below the surface of the mother. Additionally, the dynamic studies provide insight into the expected change in signal due to the both the mother and fetal heart beats. Parameters such as distance to the fetus from the detector, oxygen saturation of bother mother and fetus, patient geometry, as well as scattering properties can be varied to understand the changes in the signal. This understanding can aid future research when designing a probe that will be used on a very diverse patient population.

4 | WAVELENGTH SELECTION

Traditional pulse oximeters are inaccurate at lower oxygen saturation ranges, which would be considered normal for fetus [illegible]. One of the causes is wavelength selection. Mannheimer et. al analyzed the effect of wavelength on accuracy in pulse oximeters. They concluded that at high oxygen saturation the condition are optimal with 660 nm and 900 nm but for lower saturation 735 nm and 890 nm have better accuracy [28]. Taking into consideration wavelength dependence, Zourabian et al determined that the optimal wavelength ranges were 660-720 nm and 850-890 nm for minimum error for determining oxygen saturation [12]. These were chosen to minimize the error between calculations and maximize the sensitivity to change in oxygen saturation. The difference between these two approaches was that the former derived the optimal wavelength pair by looking at changes in blood volume and chose wavelengths that have similar penetration depth and the latter looks at wavelength dependence on saturation error [12, 28]. Fong et al. also looked at wavelength selection by performing Monte Carlo simulations at five wavelengths (700 nm, 735 nm, 800 nm, 850 nm, and 900 nm). They selected 735 nm and 850 nm as the optimal pair to obtain a stronger fetal signal for fetal depths of 2-5 cm [29].

There are a couple of considerations for wavelength selection. Since different wavelengths do not necessarily travel the same depth, the chosen wavelengths should have similar penetration depth to probe the same volume. However, if the blood oxygen saturation changes then the wavelength dependency also changes. One proposed solution is to use two pairs of wavelengths for high and low oxygen cases [12].

5 | PHANTOM STUDIES

Phantom studies have been performed in order to understand optical output for different setups in a controlled environment with a sample having known optical properties. Ramanujam et al. used glass containers with liquids of known optical properties to simulate the fetus at various depths from the surface of the mother [15]. The experiment looked at the overall light that was propagating through the phantom and did not have a pulsatile component. There were two setups: one with two glass cylinders within a tank and another with two glass boxes in a tank. The measurement probe was placed on the outer tank, which represented the uterus and varied in absorption ($\mu_a = 0.1$ cm^{-1} to 1 cm^{-1}; $\mu_s' = 5$ cm^{-1}). The next glass container represented the amniotic fluid and was filled with distilled water. The inner most container represented the fetus and had an absorption coefficient of $\mu_a = 0.15$ cm^{-1} and a reduced scattering coefficient of $\mu_s' = 5$ cm^{-1}. The cylinder and glass box that represented the fetus were 9 cm and 16 cm wide along the optical probe, respectively. Their optical probe enabled different source detector distance configuration (2.5 cm, 4 cm, and 10 cm). The two inner most containers were moved incrementally away from the optical probe to represent different fetal depths. They mention that the cylindrical setup was very dissimilar to their human data, but the box setup was more similar. They also tried different placements of the probe (by moving the inner box) and the analysis suggested that the highest sensitivity was obtained when the source was directly over the fetus' head. Continuing the phantom studies with different setups and numerical models, yielded similar results as just mentioned. Also, optimizing the source-detector separation would lead to an increase in photons travelling through the fetal head [13]. The study was combined with numerical modelling of the radiative transport equation and the diffusion equation to better understand photon migration to the fetal layer. Overall, the study demonstrated where the maximum sensitivity of the optical probe, which was with the light source over the fetal head and a fetal depth of <3 cm. These are essential parameters to know for transabdominal pulse oximetry design and placement of the probe.

One group in Germany, which has previously designed a system that combined photoplethysmographic and electrical impedance plethysmorgraphic measurements [30], developed phantoms with artificial vascular systems. The phantom consists of two tubes to represent the maternal and fetal vessel system [31]. Additionally, different materials were investigated to mimic optical properties of the mother and fetus [32]. The phantom models were improved by including a dome to better mimic the geometry of a pregnant mother, adding a sensor to measure the mechanical dilation of the artificial vessel, and improving the synthetic blood substitutes [33]. Using the modified phantom, they took measurements and implemented a comb filter to suppress the maternal heart beat and obtain just the fetal one. The filter worked even when the maternal to fetal magnitude ratio was 80 dB [25]. These types of phantoms are essential for transabdominal pulse oximetry because 1) the change in optical signals due to the fetal and maternal pulse must be studied not just the optical power alone, and 2) the phantoms provide sample data to be used to develop algorithms for separating mother and fetal signals, in which the group shows that retrieving these signals is feasible.

Fong et al. developed a continuous wave system that used two LEDs as light sources (700 nm and 850 nm) and detectors placed 4 cm and 7 cm away from the sources [34]. The closer detector was used to pick up the mother's signal and the farther detector was used to detect the fetal signal. They used four different models in order to determine if fetal signal could be detected. One model was placing a 5 cm tissue phantom with similar maternal optical properties on the forehead of a volunteer who would mimic the fetus. They were able to detect the pulse signal through the tissue phantom. The other model had a volunteer undergo exercise and another volunteer at rest. The volunteer at rest (mimics mother) placed their hand on the abdomen of the volunteer that exercised (mimics fetus) and a measurement was taken. After analyzing several signal separation techniques, they determined that the adaptive noise cancellation techniques were the most effective. These phantoms/volunteers helped to proved a pulsatile model that yielded data to test various algorithms to suppress the maternal component of the signal. In this case, adaptive noise cancellation was used.

Despite the attempts in the literature to make various phantoms to simulate complex fetus and mother system, there are few challenges to simulate accurately in a reproducible way the optical properties and physiological changes in a dynamic mother and fetus system during labor. Accurate design of phantoms can bring multiple benefits, from testing of the system on realistic optical properties, simulating the mother/fetus hemoglobin dynamics and physiological changes in a controlled way, and training of machine learning or artificial intelligence algorithms. The development and availability of the next generation of phantoms can impact the understanding and performance of transabdominal pulse oximeter research. We foresee the following type of phantoms impact the outcome of next generation transabdominal pulse oximeter development. First would be a well-controlled multilayer (e.g. two-layer) phantom system for performance assessment of the device, for example, to gain an understanding of mother only, fetus only PPG signals, contamination of superficial layer on fetus signal. Anthropomorphic fetus phantoms that consider the geometry of abdomen and fetus structure is another area that can address challenges related to different mother-fetus geometry and its influence on fetal pulsatile signal. Another critical area is the simulation of dynamic changes in the mother-fetus system using dynamic tissue-mimicking phantoms. This includes both dynamics of the photoplethysmographic signal of the combined mother-fetus system and mechanical motion artefact during labor. These phantoms development can take leverage from advancements in the literature on standardized, multilayer, functional and anthropomorphic phantoms to innovate phantoms specific for transabdominal pulse oximeter application [35-37].

6 | PRE-CLINICAL STUDIES

Fong et al also performed pre-clinical studies using a contextually aware system that incorporates knowledge about the mother's physiology, multiple detector measurements, and historical measurements of the fetal signal. They compared this approach to another in which only includes maternal noise reduction and fetal estimation blocks. The system was tested on two ewes in which the proposed method worked better than then latter method in determining the fetal heart rate [38]. Additionally, they imaged an ewe at various oxygen levels. The fetal signal was extracted by filtering the maternal component of the mixed signal by using adaptive noise cancellation. The ratio was then found by using Eq 1. By doing so they demonstrate a wide range of fetal oxygen levels of a hypoxic fetal sheep [39]. In another sheep study, the group compared their transabdominal fetal oximeter to blood measurements of a single pregnant sheep and got an r^2 value of 0.86 [40]. However, these particular methods (mother noise cancellation) may only work at shallow fetal depths where the mother component of the mixed signal is minimum and can still be filtered out. Also, since Eq. 1 typically requires calibration data to be taken, the group has used a subset of the same data to calibrate with arterial blood gas. Variability between animals has not been tested yet. If the fetus is a few centimeters below the surface the mother component may be dominant and would create an inaccurate oxygen saturation measurement. The minimum fetal depth in humans is 1.7 cm with the average being 2.9 cm [41]. The fetal depth in sheep ranges 2.4-8.2 cm [42]. Therefore, at these depths, the maternal portion of the signal may dominate the detected signal. Fetal depth is an important parameter to consider during transabdominal pulse oximetry design and poses a challenge since a technique that works at shallow depths may not work at deeper depths, or vice versa.

A pre-clinical study was performed on five pregnant sheep that underwent seven hypoxic cycles in which optical measurements were compared to oxygen saturation measurements taken from fetal blood samples [8]. The fetal head was isolated from the uterus in order to take measurements. Afterwards, the uterus was tied around the neck of the fetus and the head was placed directly under the mother's skin for more measurements. The measurements were taken from a frequency domain system with three wavelengths (675 nm, 786 nm, and 830 nm) and source-detector distances ranging from 1.8-4 cm. A finite difference, two-layer, diffusion model was used to reconstruct optical properties and obtain oxygen saturations. The normoxic (baseline) oxygen saturation of the fetus was used as *a priori* information for the algorithm. There was fairly good correlation between the blood samples and oxygen saturation obtained from optical measurements ($R = 0.76$; $p < 0.01$). However, the study had several limitations. First, since the fetal head was below the skin, the distance from the surface was 8-10 mm, which is less than a typical human fetus (>20 mm). Second, the hypoxia was controlled through the mother, so both the mother and fetus were affected. Last, one of the *a priori* information for the reconstruction algorithm came from a fetal blood sample, which would not be available in a human delivery.

Another pre-clinical study with four sheep was conducted in which hypoxia was also induced [17]. The

Table 1 List of challenges of developing transabdominal pulse oximetry

Challenge	Explanation	How to overcome	Reference
Separating mother and fetal signals	The detected signal is a mix of light that has travelled through the fetus, mother, or both. The fetal signal must be extracted. Fast Fourier transform can be used for time domain separation, but the relative intensities are difficult to obtain.	- Computational models to understand the fetal fraction of the signal.	[12, 20, 24, 26, 29]
Fetal signal hiding behind Mother harmonic in FFT.	The fetal heart rate is usually about twice the heart rate of the mother. In the Fourier domain the signal could get lost in the mother harmonic making separating the signals difficult.	- Record the fetal and mother heart rates at the same time as optical imaging. This adds to the number of inputs into an algorithm or possibly additional hardware thought.	[25, 39]
Retrieving DC component of fetal signal	In traditional pulse oximetry a ratio is used to determine oxygen saturation (Eq. XX). However, the absolute DC value is necessary to calculate the ratio. The DC value of the fetus is compromised because the detected light is also influenced by the path it took through the mother.	- Taking the ratio reduces the error - Using closer source-detector distances to establish the signal without the fetus and extrapolating the signal for further source-detector distances to obtain the mother signal for a particular detector without fetal influence.	[12, 18]
Limitations to the modified Beer-Lambert Law	The modified Beer-Lambert Law works under the assumptions that the medium is homogenous and that there is an ubiquitous change in the absorption coefficient. Both of these conditions are no longer true in the transabdominal pulse oximetry case [19].	- The two-layer modified Beer-Lambert Law	[43]
Motion Artifacts	Movement of the mother or fetus can cause artifacts in the measurement data	- Informed probe design - High pass filter to reduce breathing frequency and moving	[38]
Fetal Depth	Depth of the fetus from the surface of the mother. This can range from 1.7 mm to 2.9 cm [41]. The light power that can reach the fetus varies greatly.	- -Develop algorithms that work for large range of fetal depths, with or without fetal depth as an input.	[8]
Patient Variability	Fetal depth, body mass index, mother oxygen saturation levels, melanin content in skin, etc.	- Models with melanin or variations of fat content - Test on subjects with different BMI, skin color, etc. to determine degree of variation.	[44]

oxygen saturation was determined using a transabdominal pulse oximeter. The arterial blood saturation values obtain from the fetus were closely correlated with oxygen saturation measurements obtain from the optical probe (R^2 = 0.76). Oxygen saturation was determined using the modified Beer-Lambert law.

The pre-clinical studies have been an important step towards feasibility of transabdominal pulse oximetry because it is one way to have controlled desaturation of a fetus in utero so that a range of fetal oxygenation states can be observed. Despite the benefits of pre-clinical studies, the differences to human physiology and geometry need to be considered. While the fetal depth in sheep can be comparable to humans, the abdominal wall of sheep is more compressible compared to humans, effectively reducing fetal depth when pressing an optical probe against it. In addition, the sheep model poses a challenge due to the fact the ewe does not have one placenta, but the placenta is a polycotyledonary placenta with 70 to 100 cotyledons [45, 46]. Each of these placentomes is highly vascularized and therefore absorbing blood. The influence of these placentomes on the optical signals has not been accounted for in previous studies and should be considered further.

7 | CLINICAL STUDIES

In a clinical study with 32 patients, a non-invasive transabdominal near infrared spectroscopic probe was used to monitor women during a nonstress test (NST) [16]. The NST is used to evaluate fetal health antepartum. Continuous measurements were conducted with a probe consisting of a halogen light source and two detectors place 10 cm and 4 cm apart with 760 nm and 850 nm bandpass filters. The understanding behind the design was to use the short distance to monitor the mother and the long distance to detect the fetus. Phantom models were used to empirically determine the equations for oxyhemoglobin concentration, the ratio of oxy- and deoxy-hemoglobin concentrations, and the total hemoglobin concentration. One of the conclusions from the study was that any fetal motion artifacts were difficult to determine. At the 4 cm distance there was an increase in oxyhemoglobin concentration and volume but a decrease in the saturation during contractions, which contradicts what would be expected i.e., a decrease in blood volume and oxygenation. For the 10 cm source detector distance there was a similar trend as just described, which is also physiologically contradictory with what was expected. Yet, the study concluded that photon migration is possible with a source detector distance of 10 cm.

Continuing from a similar setup, there was a study with 19 pregnant mothers that underwent NST in which both fetal heart rate and uterine contractions were simultaneously monitored [15]. A few modifications were made to the previously mentioned system. A halogen (20 W) and two tungsten lamps (0.575 W each) were placed 10 cm and 2.5-4 cm away from the photodetectors, respectively on a flat probe that was placed on the mother's abdomen. A signal to noise ratio of about 50 was achieved for both large and small source detector distances. Again, there was difficulty determining artifacts from fetal motion. The study determined that the fetus was more absorbing than the mother, amniotic fluid was minimal between the maternal tissue and the fetus, and the probe had maximum sensitivity when the source was placed over the fetal head. Finally, the probe was sensitive up to fetal depths of 3 cm.

In another clinical study with 6 pregnant women (gestation age >36 week), a continuous wave system with 3 LEDs (735 nm, 805 nm, and 850 nm) were used to assess the oxygen saturation during a checkup or NST (antepartum) [14]. The probe had source detector separations between 7 cm and 11 cm. Fetal heart rate was obtained via a Fourier transform of the detected light intensities at the three wavelengths. The fetal heart rates varied from 132 bpm to 165 bpm. The mean fetal oxygen saturation values varied from 50% to 74% with an average of 61% +/- 14.8%. While these values fell into known ranges of fetal oxygenation, methods to evaluate the true oxygen saturation of the fetus were not used for this study. Ideally, transvaginal oxygen saturation measurements can be taken but only during labor and were not possible for this study.

A group in Malaysia developed a system to obtain transabdominal fetal heart rate measurements with one LED at 890 nm (55 mW) [47]. The source-detector distance was 4 cm in order to obtain a strong signal with an estimated 70% of the signal from the fetus based on previous Monte Carlo simulations [20]. The mother had a reference probe on her finger to obtain only her heart rate. Synchronous detection and adaptive filtering techniques were used to obtain fetal heart rate. Six pregnant women were measured. The fetal heart rate was detectable with acceptable accuracy and a maximum error of 4% compared to ultrasound readings. The probe position and the possible presence of motion artifacts may have an effect on the signal [47]. Since then, this group has performed other studies to improve design [48, 49], ensure light exposure safety to the fetus [50], and a theoretical calibration curve for oxygen saturation [51].

As described above, there have been several clinical studies using transabdominal pulse oximetry that have demonstrated feasibility of the technique in human patients. They are able to obtain sufficient signal and have adapted various techniques to separate mother and fetal signals. However, there are still several challenges transabdominal pulse oximetry faces before it can be realized as a clinically relevant device.

8 | CHALLENGES

While many of the above-mentioned studies have demonstrated feasibility towards transabdominal fetal pulse oximetry, the realization of the technology has not occurred. There are still several challenges that must be overcome to translate the technology into the clinic (see Table 1).

One of the first challenges has been separating the mother and fetal signal. The fetus has a higher heart rate than a grown adult, which in most cases can be separated using Fourier transforms. However, occasionally, the fetal heartrate will lie on the harmonics of the mother (i.e. Mother is 1 Hz and the fetus is 2 Hz), and thus difficult to separate from the mother harmonic signal [38]. Optically, the measured signal is composed of both mother and fetal components. The original DC portion of the fetal pulse without the mother component may not be retrievable [12]. Additionally, using the modified Beer Lambert Law or the multilayer modified Beer-Lambert Law may not be possible at centimeter depths, since the equation loses accuracy at activation sights deep in the medium [43]. The implication is that it may not be possible to use the modified Beer-Lambert law without further modifications because the fetus is usually centimeters below the surface of the mother's abdomen.

Another significant issue is movement artifacts that can be introduced into the measurement. This includes the mother's breathing or general movement during labor. Additionally, the fetus could also move *in utero* and cause artifacts. The movement could cause a change in fetal depth, which has been an important parameter in the amount of light that reaches the fetus and then is collected [24, 29].

Fetal depth is another important factor to consider when developing transabdominal fetal pulse oximetry. Not all fetuses are at the same depth from the surface of the mother. This parameter may be known or unknown depending on the protocol used. This places a challenge for developing an algorithm for determining SaO_2. For example, fetal depth can only be determined with ultrasound imaging. However, the fetus is usually centimeters deep from the surface of the mother posing another challenge: enough light reaching the fetus and then being detected. Sufficient signal to noise is necessary in order to process the fetal pulse.

Including fetal depth, other patient variability will pose challenges for developing a robust algorithm for determining oxygen saturation. For example, the BMI of the mother, her oxygen saturation levels, melanin content in skin, etc. will affect how the light travels through the abdomen. Additionally, variations of the fetus or uterine environment can affect the signal such as the amount of amniotic fluid present, melanin content in the skin, placement of the head, etc.

For future research, time of flight might provide valuable information of photon migration through mother and fetus, as well as give clues to how deep the photons have travelled. Additionally, while the technology has shown to be feasible in detecting fetal signals, there needs to be more research on how to extract the oxygen saturation accurately.

9 | CONCLUSION

Transabdominal pulse oximetry has the ability to be a powerful tool to aid clinicians in making decisions about when to perform C-section deliveries during labor. By having a more accurate metric, such as fetal arterial oxygen saturation, unnecessary fetal trauma or unnecessary C-section deliveries can be avoided. There has been significant research to show the feasibility of the method and some of the design parameters that are necessary to make the technology work. However, this method still faces challenges it must overcome in order to make it a more viable clinical technology to be used at a very critical moment such as birth. Through utilizing computer modelling and phantom modelling, a better understanding of the measurements can be acquired. The multiple preclinical and clinical studies have demonstrated feasibility. Future studies should focus on robust methods of determining fetal arterial oxygen saturation from a diverse population.

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AUTHOR CONTRIBUTIONS

Jacqueline Gunther wrote the majority of the paper. J.G. and B.J. performed the literature search. All the authors discussed the benefits and challenges of the various techniques. Additionally, all the authors have contributed to the text.

FINANCIAL DISCLOSURE

Sanathana Konugolu Venkata Sekar and Stefan Andersson-Engels have financial interests in BioPixS Inc, a company specializing in tissue optical phantoms for measurement standardization.

CONFLICT OF INTEREST

Jana M. Kainerstorfer is a consultant for Raydiant Inc. and has financial interests in the company. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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Graphical Abstract for Table of Contents

Transabdominal fetal pulse oximetry works by illuminated a spot on the abdomen of the mother and detecting the output light over time in order to analyze the time traces. After obtaining the time signals from the system, various algorithms can be applied to determine the oxygen saturation (SaO_2%) of the fetus non-invasively.