Raydiant Oximetry, Inc.

KEEPING MOTHERS AND BABIES SAFE DURING CHILDBIRTH

The Past, Present and Future of Fetal Oximetry

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ABSTRACT: **Raydiant Oximetry, Inc. is developing a non-invasive fetal pulse oximeter to more accurately diagnose oxygen deprivation which could potentially lead to fetal injury during labor. Over 84% of all laboring women experience a indeterminate (Category II) fetal heart rate tracing during labor, yet 99% of their newborns do not suffer birth asphyxia. Furthermore, fetal heart rate monitoring fails to identify 50% of the newborns born with significant metabolic acidosis. With maternal mortality rates on the rise in the United States from the overuse of cesarean deliveries, the need for a novel intrapartum fetal monitor remains a significant unmet need.**

INTRODUCTION: Raydiant Oximetry, Inc. is developing a novel and completely non-invasive fetal pulse oximetry device to fundamentally transform how fetuses are monitored during labor. Pulse oximetry exists in virtually every clinical setting as a means to assess oxygen levels. It is used to diagnose oxygen deprivation, which can lead to organ and brain injury in extreme cases. Yet, no such technology exists for fetuses, especially during the physiologically stressful stages of labor. Current technology, called cardiotocography (CTG), is used to monitor the fetal heart rate tracing in relation to uterine contractions over time. This technology is used annually on over 3.6 million laboring women in the United States but is antiquated, difficult to interpret, and a surrogate for the true measure of the fetus's well being. In the absence of reliable data and in a litigious environment, physicians must take a conservative management approach, which has led to a large increase in cesarean delivery rates as a means to rescue fetuses at risk for severe metabolic acidosis. While seemingly innocuous, cesarean deliveries are associated with significant complications for both mother and newborn, including maternal mortality, which has risen dramatically in the United States. Furthermore, CTG monitoring leads to false negatives, where an at riskfetus is not detected and the resulting outcomes are devastating. The need for a better fetal monitor has plagued the obstetrical community for over 50 years.

FETAL MONITORING & CTG: Labor is physiologically stressful to the fetus. When the uterus contracts to expel the fetus through the birth canal, there is a temporary decrease in uterine blood flow and fetal perfusion due to a constriction of the uterine arteries. In addition, as the fetus descends through the pelvis, the umbilical cord can be compressed, and result in reduced blood flow to the fetus. Over 99% of fetuses tolerate uterine contractions and the birthing process, but approximately 1% of fetuses develop hypoxia and subsequent metabolic acidosis from repeated uterine contractions that ultimately leads to the development of hypoxic ischemic encephalopathy (HIE) [1].

Although this form of new-born neurological injury is rare, the consequences are completely devastating, resulting in significant cognitive and motor disabilities. The incidence of HIE is estimated up to 9 babies per 1000 term births. With 4.1 million annual births in the United States, approximately 36,900 babies are affected annually by this condition. Since the need for life-long care is an unfortunate reality for many of these children, developing a solution for this unmet clinical need is paramount.

Since the 1800s, a slowing of the fetal heart rate (fetal bradycardia) has been recognized as a predictor of significant fetal morbidity and mortality. In 1968, continuous cardiotocography (CTG) monitoring was developed to continuously monitor for potential fetal injury.. If a physician could identify the fetus at risk for developing hypoxic ischemic encephalopathy, an intervention such as a cesarean delivery could rescue the fetus before irreversible brain injury occurs. However, significant limitations exist with this technology:

I. The interpretation of the CTG tracings is subjective. In a large study, asking five physicians to interpret the same fetal heart rate tracing led, on average, to four distinct conclusions [2]. Further, when asked one year later, the physician would change his/her interpretation of the fetal heart rate tracing 50% of the time. Even attempts to utilize machine learning and artificial intelligence for CTG interpretation have failed to accurately and reliably detect fetus at risk for metabolic acidosis [3].

II. A recent landmark study has shown that CTG interpretation among experts has a 50% false negative rate for detecting fetal distress [4]. This means that 50% of fetuses in distress had heart rate tracings that were interpreted as normal. Consequently, the physician had no indication that the fetus needed to be rescued and devastating results to the newborn followed.

III. It is estimated that 84% of laboring women will experience a Category II fetal heart rate tracing which is indeterminate on its own and requires evaluation, continued surveillance and reevaluation [5]. Obstetrical providers struggle to determine which category II fetal heart rates will lead to newborn injury, as over 99% of these Category II tracings are false positives.

These limitations have led physicians to perform more and more cesarean deliveries, many of which are deemed medically unnecessary. In fact, cesarean delivery rates have increased 400% over the past 40 years in the United States with no improvements of newborn neurological injury rates [6]. Approximately 1/3 of laboring women will receive a cesarean delivery for the birth of her baby and according to the World Health Organization, 50% of these cesarean deliveries are medically unnecessary [7]. It is estimated that 24% of all cesarean deliveries performed in the United States are a result of abnormal fetal heart rate tracings and 60% of all emergency cesarean deliveries are performed for abnormal fetal heart rate tracings [8,9]. This translates into 300,000 major abdominal surgeries per year.

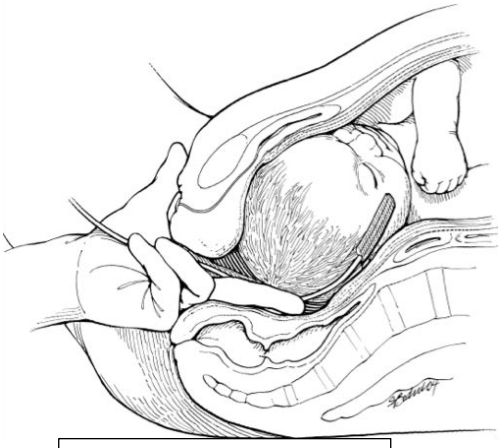
C-SECTIONS & ASSOCIATED RISKS: Cesarean deliveries are associated with morbidity and mortality to the mother, especially when repeated for subsequent pregnancies, which accounts for over 90% of deliveries in the United States [10]. Complications can include post-operative wound infections, thromboembolic events and injury to the bowel & bladder [11]. With each cesarean delivery, the risk of maternal hemorrhage increases because of conditions such as uterine rupture, placenta previa and placenta accreta. A mother with a history of three or more cesarean deliveries has a 60% chance of developing an abnormal placental condition that could lead to hemorrhage and death [12]. Over the past 15 years, maternal mortality in the United States has increased dramatically, which ranks the US highest in maternal mortality of all developed nations [13]. This is largely due to maternal hemorrhage as the cause of death. While the reasons behind increasing maternal mortality are multifactorial, most experts agree that reducing primary cesarean delivery rates and subsequent repeat cesarean deliveries will reduce the incidence of abnormal placentation and subsequent morbidity/mortality associated with maternal hemorrhage.

Cesarean deliveries are also associated with significant newborn morbidity & mortality. The literature shows that babies born by cesarean delivery are more likely to require care in the newborn intensive care unit (NICU) and have an increased incidence of difficulty breast feeding, sudden infant death syndrome (SIDS), asthma, type 1 diabetes, Crohn's disease, autism and childhood obesity [13,14]. A vaginal delivery protects the newborns by expelling amniotic fluid of out of the lungs and inoculating the fetus with a protective microbiome.

Furthermore, medical malpractice litigation is notorious in obstetrics and a concern for all clinicians in the field. In a 2018 analysis of 1,298 obstetrical cases from 2012-2016, $725 million dollars of payout resulted from this case series with intrauterine fetal hypoxia as the most common diagnosis for the successful lawsuit [15]. Given all of the issues described above, it is well recognized that a novel technology that can reliably detect potential fetal injury during labor would help improve both newborn and maternal health. The Nellcor Corporation recognized this need in the 1990s and commercialized a fetal pulse oximetry (FPO) device, marketed as the OxiFirst.

THE NELLCOR FETAL PULSE OXIMETER: Pulse oximetry is a technology that calculates the oxygen saturation levels of hemoglobin in the arterial system by measuring the light reflection. Hemoglobin bonded to oxygen absorbs light less readily than hemoglobin that is not bonded to oxygen. By comparing the ratio of light reflection over multiple wavelengths of light, the percentage of hemoglobin bonded to oxygen (i.e. oxygen saturation) can be calculated. Traditional pulse oximetry transmits light through an appendage such as a fingertip or an earlobe. Because no such appendage is available from a fetus in-utero, the Nellcor Corporation developed a fetal pulse oximeter that could reflect light off the fetal surface [16].

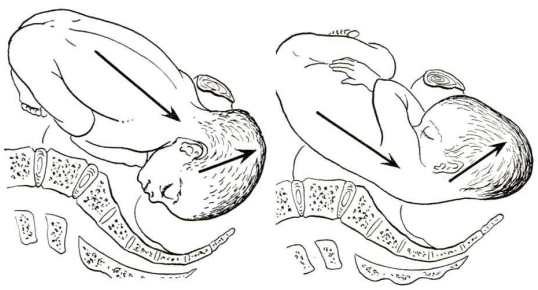
Nellcor's OxiFirst fetal sensor was inserted through the birth canal and wedged between the fetus's cheek, temple or forehead and the uterine wall. In 2000, the Nellcor Corporation applied to the FDA for approval, indicating that the prospective use of OxiFirst during labor and delivery could reduce cesarean delivery rates. To support those claims, Nellcor completed a randomized, controlled study in 1010 patients where the control group was monitored with traditional electronic fetal heart rate monitoring (CTG) and the study cohort was monitored with electronic fetal heart rate monitoring plus continuous fetal pulse oximetry [17]. The results demonstrated a 50% reduction in cesarean delivery rates when CTG + FPO was used to evaluate non-reassuring heart rates, a clear validation that fetal pulse oximetry added clinical value. Unfortunately, having the device wedged in the birth canal additionally led to a 100% increase in cesarean deliveries from dystocia, a condition where the fetus stops progressing through the birth canal.



Nellcor OxiFirst Sensor

The FDA granted Nellcor PMA approval to market the OxiFirst device as an adjunct monitor to CTG in the presence of a nonreassuring fetal heart rate pattern and required the Nellcor Corporation to conduct a post-market analysis to investigate the increased incidence of dystocia [18]. Subsequently, Kuhnert et al. performed a second clinical trial with patients randomized to receive continuous fetal pulse oximetry. In this study, there was a reduction of cesarean delivery rates for non-reassuring fetal heart rate tracings with an increase for cesarean deliveries from dystocia [19]. A third clinical trial called the FOREMOST trial enrolled 600 women randomized to receive continuous fetal pulse oximetry and again this study yielded a similar increase in cesarean deliveries from dystocia [20].

So why was there an increase in dystocia from the continuous use of the OxiFirst fetal pulse oximetry? Vidaeff et al. suggested that there was an increase in persistent occiput-posterior position with the continuous use of the OxiFirst sensor [21]. As the fetus descends down the birth canal, the head also rotates in a cork screw fashion from occiput-posterior to occiput-anterior and perhaps the sensor that was wedged between the fetus's cheek and the uterine wall mechanically prevented the fetus from rotating. If the fetus's head remains in a persistent occiput posterior position, this position is associated with dystocia and an increased need for cesarean delivery [22]. Porreco et al. also reported an increased rate of occiput-posterior in the cohort of patients requiring cesarean delivery for dystocia but hypothesized that nonreassuring fetal heart rate tracings were a result of dystocia [23]. Finally, in a study published in 2009, fetal pulse oximetry was used in an intermittent fashion with a treatment protocol instead of continuously usage and the results demonstrated a decrease in cesarean delivery rates for non-reassuring fetal heart rate tracings with **no increase** of cesarean deliveries from dystocia [24]. By using the OxiFirst sensor intermittently, the presumed mechanical obstruction from continuous usage was not causing a persistent occiput-posterior position or an increase of dystocia.



With an OP there is deflexion of the baby's head and so there is a larger diameter to stretch the vaginal entrance.

During the same time period, the National Institute of Child Health and Development (NICHD) sponsored a very large randomized clinical trial (FOX Trial) at 14 US academic medical centers. In this study, all 5,341 patients had a fetal pulse oximeter placed for continuous monitoring, but clinicians only saw the measurements for 2,629 patients randomized into the open group [25]. The study design did not provide a protocol for clinicians with guidelines on how to manage patients using the oxygen saturation results provided by OxiFirst [25]. Without surprise, there was no change in cesarean delivery rates between the control and study groups because the study did not teach clinicians how to use the fetal pulse oximeter results. There was also no difference in dystocia rates between the two groups as both groups had the OxiFirst inserted continuously. This study was published in the New England Journal of Medicine despite the flawed study design and several prominent organizations such as the American College of OB/GYN (ACOG) and the Cochrane database prematurely concluded that fetal pulse oximetry offers no value to the clinician or patient [26,27,28].

THE TRUE VALUE OF FETAL PULSE OXIMETRY: The true value of this technology was subsequently identified when human studies showed that the detection of fetal hypoxia from fetal pulse oximetry could predict the development of metabolic acidosis in the newborn. It is well understood that when the fetal oxygen saturation falls below 30% in-utero, the fetus has an inadequate oxygen supply and is at risk for developing metabolic acidosis from anaerobic lactate production [29,30,31]. Newborn metabolic acidosis is measured by analyzing the pH of blood samples taken from the umbilical cord. As the blood becomes more acidic, the pH falls to a critical level, with metabolic acidosis defined by a pH of less than 7.2. If the pH continues to fall below 7.0, the fetus is at a significant risk for seizures, hypoxic ischemic encephalopathy or even death. This knowledge of fetal biology used in combination with fetal pulse oximetry has demonstrated that when oxygen saturation falls below 30% for at least 10 minutes or two uterine contractions, the umbilical blood pH begins to fall towards levels of acidosis of concern [30]. Furthermore, the fetus that does not experience a hypoxic event of the oxygen saturation falling below 30% for great than 10 minutes is unlikely to develop metabolic acidosis.

Using these parameters, several studies have now clearly demonstrated the true value of fetal pulse oximetry. In a 400-patient study, Seelbach-Göbel et al. found that the OxiFirst fetal pulse oximeter had a 100% sensitivity, an 81% specificity and a 51% positive predictive value for detecting newborn metabolic acidosis [31].

In 2010, Nonnenmacher et al. reported similar conclusions in a 101 patient study, where fetal pulse oximetry had a 92.9% sensitivity, an 87.4% specificity and a positive predictive value of 54.2% for detecting newborn metabolic acidosis [32]. These results are in stark contrast to electronic fetal heart rate monitoring, which has a 93% sensitivity, a **29%** specificity and a positive predictive value of **2.6%** for detecting newborn metabolic acidosis [33].

Detection of Fetal Metabolic Acidosis

	Sensitivity	Specificity	PPV
CTG alone (Low)	93%	29%	2.6%
FPO (Seelbach-Göbel)	100%	81%	51%
FPO (Nonnenmacher)	92.9%	87.4%	54.2%

Unfortunately, during the same time, the Nellcor Corporation was engaged in a series of mergers and acquisitions. In 1997, Mallinckrodt acquired the Nellcor Corporation and in July 2000, Tyco International acquired Mallinckrodt [34,35]. Twenty years ago, the OxiFirst device achieved over $1 million dollars in European sales in the 1st year after CE mark and within 2 years of FDA approval, OxiFirst was being used in 10% of all labor units in the United States [36,37]. Despite these markers of initial commercial success, the perinatal business unit was closed down in 2002 as a business decision by Tyco to focus on the profitable business lines within the Nellcor portfolio. Eventually Tyco International spun off the health care business to Covidien in 2007 and then Medtronic acquired the Covidien assets in 2015 [38,39].

To this day, a commercial fetal pulse oximetry device has not been successfully marketed while the significant unmet clinical need continues to persist. Multiple experts in obstetrics opine that if fetal pulse oximetry continued to be marketed beyond 2002, the technology would have achieved significant clinical adoption. The need for this technology is even more pressing today than it was in the early 2000s. For the past 15 years, maternal mortality has steadily increased in the United States, with the U.S. ranking 46th in the world for maternal mortality behind countries like Saudi Arabia and Kazakhstan [40]. Much attention has recently been given to the increasing maternal mortality rates and the disparities in maternal care. The President of the United States signed historic legislation in 2018 to prevent maternal deaths. ACOG published a consensus statement in 2014 on the "Safe Prevention of the Primary Cesarean Delivery" [41,42].

THE RAYDIANT OXIMETRY FETAL PULSE OXIMETER:

Raydiant Oximetry**, Inc.** is working to develop the tool that clinicians have needed for over 50 years – a fully non-invasive fetal pulse oximeter that provides fetal oxygen saturation monitoring without adversely affecting the birthing process. **LUMERAH™** is a completely external, non-invasive sensor that is placed on the maternal abdomen. **LUMERAH** can be used earlier in the labor process than OxiFirst because **LUMERAH** does not require cervical dilatation for insertion, rupture of the amniotic sac or the fetus to have descended.

Raydiant Oximetry received breakthrough status by the FDA in October of 2018 to expedite market approval of **LUMERAH** through a proposed indication for use that **"**The **LUMERAH** device is a non-invasive fetal pulse oximetry measurement device for use in adjunct with fetal heart rate monitoring to aid clinicians in the detection of potential fetal injury resulting from hypoxia.**"** Raydiant Oximetry intends to develop marketing claims that **LUMERAH** has improved diagnostic accuracy for the detection of fetal metabolic acidosis when used with CTG than CTG monitoring technology alone and will design a pivotal study to support such claims. Based on a meta-analysis of 500 patients from the Seelbach-Göbel & Nonnenmacher studies, Raydiant Oximetry expects that **LUMERAH** can achieve a minimum specificity of at least 81% for the detection of fetal metabolic acidosis, which is in stark contrast to the 29% specificity of CTG monitoring [31,32,33].

With the improved diagnosis of fetuses at risk for severe oxygen **deprivation**, it is proposed that the prospective use of **LUMERAH** could lead to a reduction of emergency Cesarean delivery rates for fetuses suspected to be at risk for severe metabolic acidosis and the eventual decrease of maternal morbidity/mortality from the overuse of cesarean deliveries. In addition, the improved diagnosis of fetuses at risk for severe metabolic acidosis through the **LUMERAH** technology will improve neonatal cord blood gases at birth, reduce NICU admissions and the NICU length of stay. Furthermore, the neonatal chronic morbidity that is associated with cesarean delivery may also be reduced from a reduction in emergent cesarean delivery.

Experts in obstetrics and maternal fetal medicine have written that they hope the "original promise of fetal pulse oximetry will one day be fulfilled." Raydiant Oximetry, Inc. intends to fulfill that promise and ultimately improve outcomes for mothers and babies during childbirth by commercializing the **LUMERAH** technology.

REFERENCES:

1. Graham, Ernest M., et al. "A systematic review of the role of intrapartum hypoxia-ischemia in the causation of neonatal encephalopathy." *American journal of obstetrics and gynecology* 199.6 (2008): 587-595.
2. Sabiani, Laura, et al. "Intra-and interobserver agreement among obstetric experts in court regarding the review of abnormal fetal heart rate tracings and obstetrical management." *American journal of obstetrics and gynecology* 213.6 (2015): 856-e1.
3. Balayla, Jacques, and Guy Shrem. "Use of artificial intelligence (AI) in the interpretation of intrapartum fetal heart rate (CTG) tracings: a systematic review and meta-analysis." Archives of gynecology and obstetrics (2019): 1-8.
4. Clark, Steven, et al. "The limits of electronic fetal heart rate monitoring in the prevention of neonatal metabolic acidemia." *American journal of obstetrics and gynecology* 216.2 (2017): 163-e1.
5. Jackson, Marc, et al. "Frequency of fetal heart rate categories and short-term neonatal outcome." *Obstetrics & Gynecology*118.4 (2011): 803-808
6. Sameshima, Hiroshi, et al. "Unselected low-risk pregnancies and the effect of continuous intrapartum fetal heart rate monitoring on umbilical blood gases and cerebral palsy." *American journal of obstetrics and gynecology* 190.1 (2004): 118-123.
7. https://www.who.int/mediacentre/news/releases/2015/caesarean-sections/en/
8. Molina, George, et al. "Relationship between cesarean delivery rate and maternal and neonatal mortality." JAMA 314.21 (2015): 2263-2270.
9. E. Barber, et al. Contributing indications to the rising cesarean delivery rate. Obstet Gynecol, 118(1): 29–38, 2011.
10. ACOG Committee on Obstetric Practice. "Induction of labor for vaginal birth after cesarean delivery." *Obstetrics & Gynecology* 99.4 (2002): 679-680.
11. Villar J, Carroli G, Zavaleta N et al. Maternal and neonatal individual risks and benefits associated with caesarean delivery: multicentre prospective study. BMJ 335(7628), 1025, 2007.
12. Silver, Robert M., and D. Ware Branch. "Placenta accreta spectrum." *New England Journal of Medicine* 378.16 (2018): 1529-1536.
13. Slomski, Anita. "Why Do Hundreds of US Women Die Annually in Childbirth?" *JAMA* 321.13 (2019): 1239-1241.
14. M.J. Hyde and N. Modi. The long-term effects of birth by caesarean section: The case for a randomised controlled trial. Early Human Dev, 88(12), 943-949, 2012M-C. Arrieta, LT. Stiemsma, N. Amenyogbe, EM. Brown and B. Finlay. The intestinal microbiome in early life: health and disease. Front. Immunol. 5:427, 2014.
15. Copyrighted by and used with permission of The Risk Management Foundation of the Harvard Medical Institutions Incorporated, all rights reserved.
16. Garite TJ et al. A multicenter controlled trial of fetal pulse oximetry in the intrapartum management of nonreassuring fetal heart rate patterns. Am J Obstet Gynecol. 2000;183:1049-1058.
17. https://www.accessdata.fda.gov/cdrh_docs/pdf/P990053A.pdf
18. Kuhnert M, Schmidt S. Intrapartum management of nonreassuring fetal heart rate patterns: a randomized controlled trial of fetal pulse oximetry. Am J Obstet Gynecol. 2004;191:1989–1995.
19. East CE et al. The effect of intrapartum fetal pulse oximetry, in the presence of a nonreassuring fetal heart rate pattern (the FOREMOST trial). Am J Obstet Gynecol. 2006; 194:606e1–606e16.
20. Vidaeff AC. Fetal pulse oximetry: 8 vital questions. OBG Manag. 16(3): 28-44, 2004.
21. M. Fitpatrick, K. McQuillan, and C. O'Herlihy. Influence of persistent occiput posterior position on delivery outcome. Obstet Gynecol. 98(6): 1027-31, 2001
22. Porreco RP, Boehm FH, Dildy GA, et al. Dystocia in nulliparous patients monitored with fetal pulse oximetry. Am J Obstet Gynecol. 2004;190:113–117.
23. Caliskan E, Cakiroglu Y, Corakci A, et al. Reduction in caesarean delivery with fetal heart rate monitoring and intermittent pulse oximetry after induction of labour with misoprostol. J Maternal Fetal Med. 2009;22:445–451.
24. Bloom SL, Spong CY, Thom E, et al. Fetal pulse oximetry and cesarean delivery. NEJM. 2006; 355:2195–2202.
25. American College of Obstetricians and Gynecologists. Committee opinion: fetal pulse oximetry. Number 258, September 2001. Obstet Gynecol. 2001;98:523-524.
26. East CE, Chan FY, Colditz PB, et al. Fetal pulse oximetry for fetal assessment in labour. Cochrane Database Syst Rev 2007;18:CD004075
27. Garite, Thomas, et al. "Fetal pulse oximetry." *Obstetrics & Gynecology* 99.3 (2002): 514-515.
28. Nijland R, Jongsma HW, Nijhuis JG, et al. Arterial oxygen saturation in relation to metabolic acidosis in fetal lambs.
29. Kuhnert M, Schmidt S. Intrapartum management of nonreassuring fetal heart rate patterns: a randomized controlled trial of fetal pulse oximetry. Am J Obstet Gynecol. 2004;191:1989–1995.
30. Dildy GA, van den Berg PP, Katz M, et al. Intrapartum fetal pulse oximetry: fetal oxygen saturation trends during labor and relation to delivery outcome. Am J Obstet Gynecol. 1994;171:679–68.
31. Seelbachr Göbel, Birgit, et al. "The prediction of fetal acidosis by means of intrapartum fetal pulse oximetry." American Journal of Obstetrics and Gynecology 180.1 (1999): 73-81.
32. Nonnenmacher, et al., 2010. Predictive value of pulse oximetry for the development of fetal acidosis. *Journal of perinatal medicine*, *38*(1), pp.83r 86.
33. Low JA, Victory R, Derrick EJ. Predictive value of electronic fetal monitoring for intrapartum fetal asphyxia and metabolic acidosis. Obstet Gynecol. 1999;93:285r 291.
34. https://www.wsj.com/articles/SB869707932790765000
35. https://www.wsj.com/articles/SB962227324727281101
36. Personal communication with Nellcor management, 2019
37. Dildy GA. A guest editorial: fetal pulse oximetry. Obstet Gynecol Surv. 2003;58:225-226
38. https://www.mddionline.com/tyco-healthcare-become-covidien
39. https://www.reuters.com/article/us-covidien-medtronic-inc/medtronic-to-buy-covidien-for-42-9-billion-rebase-in-ireland-idUSKBN0ER03420140616
40. https://www.cbsnews.com/news/maternal-mortality-an-american-crisis/
41. Preventing Maternal Deaths Act of 2018. H.R. 1318. 115th Congress, 12/21/2018
42. Caughey, Aaron B., et al. "Safe prevention of the primary cesarean delivery." American journal of obstetrics and gynecology 210.3 (2014): 179-193.
43. Yam, John, Selina Chua, and S. Arulkumaran. "Intrapatum fetal pulse oximetry. Part 2: Clinical application." *Obstetrical & gynecological survey* 55.3 (2000): 173-183.

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