HOW SMALL IS TOO SMALL?`

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I was a new Assistant Professor at UCLA when I got pregnant for the first time in 1986. I was labeled a “high-risk pregnancy” because of my age. In the 1980’s, being pregnant in one’s thirties was considered very high-risk. And “high-risk” meant that I could have many complications, including premature delivery. And since I was a neonatologist, a specialist who cares for premature babies, I knew only too well all the complications that a premature baby could have. And in 1986 the survival rate for premature babies was not 100% or even close. Depending on how premature the baby was, the mortality rate could be quite high. I was told to take it easy by my obstetrician but I was worried about the “disapproval” of my colleagues if I took it easy in the very competitive environment of academic medicine. So, I continued to work 80-hour weeks like everyone else, on my research, in the hospital, and also traveled to research conferences. I did not tell my colleagues that I was pregnant.

And as fate would have it, I went into premature labor. I was just a little over 7 months into my pregnancy when full term is 9 months. “No, no, no, no!” my brain screamed, “This is too early!”. I immediately imagined the worst. My baby struggling for his breath, staying in the neonatal intensive care unit, for weeks or even months, suffering damage to his lungs and brain, and maybe, not even surviving. In my hospital bed, as I lay laboring, I wracked my brain, “What can I do to help my baby?”

To survive, premature babies minimally need reasonably mature lungs, nutrition, and external heat to maintain a normal body temperature. In the 1880s, French politicians, fearing that they would not have sufficient soldiers to fight their wars, because of the dismal French infant mortality rate, introduced a government mandate to develop methods to save the lives of premature babies. Soon, in 1896, French physicians invented the closed infant incubator.

The following year, in 1897, Martin Couney brought the incubator from France to the US, at a time when premature babies were not even allowed to stay in most hospitals in the US. These machines provided heat to these little babies and kept them alive. But physicians and hospitals in America did not welcome it. So, he held exhibits of premature infants in incubators at various expositions and World Fairs. His “Incubator-Baby Side Show” consisted of 8-10 premature babies inside incubators that were infused with heated air. The parents were poor without resources to get their babies any specialized care, so they offered them up to Couney. The audience bought 25 cent tickets and left with either great indignation that the babies were being treated as “animals in a zoo” or just sheer amazement.

For many years at Coney Island, New York, his exhibit of premature babies was among those that formed the FREAK SHOW, with attractions such as the bearded woman, the stem man who had no arms and legs, and the round woman who suffered from morbid obesity. An aspiring young actor named Archibald Leach worked as a barker outside the exhibit yelling "Don't pass the babies by!" He later achieved fame under his stage name Cary Grant.

Martin Couney brought his Incubator-Baby Side Show to Chicago first in 1893, to the World’s Columbian Exposition and then again in 1933, to the Chicago Century of Progress Exposition. The Baby Incubator Show was placed next to Sally Rand’s burlesque show. When the police raided her show and her fan dancers, she protested, “Wait a minute! My girls are wearing more clothes than the babies next door!” Over his life time it is estimated that Couney saved the lives of over 7000 premature babies and he had many grateful parents.

Two eminent Chicagoans played key roles in improving the care of premature babies. In the early 1900s, most hospitals and physicians in the US perceived the incubator as something superfluous and expensive. Physicians would sometimes place warm bricks in the cradles next to the premature babies to provide heat, or raise the temperature inside the room where the babies were kept to ninety degrees or higher. Dr Joseph DeLee, an obstetrician in Chicago, established the Chicago Lying-in Hospital in 1895, which is now the University of Chicago

Hospital and created the first “premature ward” with incubators in it. Dr. DeLee is recognized as the father of modern Obstetrics in the US.

An article in the San Francisco Chronicle in 1902 entitled "What Becomes of the Incubator Babies?" read "Nine years ago, in 1893, one of the curiosities of the World's Fair at Chicago was a baby incubator in full operation, taking care of a prematurely born baby, one of those helpless little changelings brought into the world alive and breathing before its time. It was exhibited as a curiosity, a thing of wonder. Today, to raise a prematurely born baby without the assistance of an incubator would be like dressing a wound without antiseptic precaution. This change demonstrates the swift movement of scientific improvements …...".

In 1902, Dr Julian Hess, a Pediatrician, came to Chicago and slowly took over the care of premature babies from the Obstetricians. He is recognized as the father of Neonatology. He became close friends with Martin Couney and designed the first US built incubator in 1914. His Neonatal Intensive Care Unit at Michael Reese hospital became the premier unit in the country where physicians from all over the US and abroad came to learn to care for premature babies.

Dr. Hess identified all babies born weighing less than 5.5 pounds at birth as “Low Birth Weight” babies and at his insistence, in 1935, the American Academy of Pediatrics adopted this classification, which was followed soon by the World Health Organization. He insisted that the birth of all “Low Birth weight” babies be reported to the local State Board of Health. If the baby could not receive appropriate care at the community hospital, the baby had to be transported to a tertiary center in a special transport incubator. This started the practice of “Regionalized Care” which is the standard now. Dr. Hess was the Head of the Department of Pediatrics at the University of Illinois at Chicago for over 40 years. Following in the footsteps of this giant, a little over a 100 years later I came from UCLA to be the Head of Pediatrics at the University of Illinois at Chicago.

In the 1930s, oxygen gained a reputation for easing the breathing difficulties of premature babies with immature lungs. Pure oxygen was piped into the closed-door incubators and it did

improve the survival of premature babies. However, its unregulated use in high concentrations and for prolonged periods of time turned out to be a disaster. In 1942, the *American Society of Ophthalmology* brought attention to an increasing incidence of blindness in premature babies. A decade later, a large, multi-hospital study on the effects of oxygen in premature babies provided definitive evidence that oxygen use was the cause of the blindness. Oxygen use was immediately curtailed throughout the world and rates of blindness dropped dramatically. But without oxygen treatment, deaths in premature babies rose again.

On August 7, 1963, a baby boy was delivered by cesarean section in Otis Air Force base hospital. He was born 5 and half weeks too early and weighed only 4 lbs. and ten and a half ounces. Jackie and John Kennedy wanted the best possible care for their son, Patrick, and so he was air lifted to Boston Children's Hospital, where the doctors did everything they could for him, including giving the baby pure oxygen under high pressure, an untested therapy at that time. But he died 39 hours later. The cause of death was Hyaline Membrane Disease, a condition where the lungs are immature, cannot hold air in them and turn solid like a liver. Full term babies are born with mature lungs and they fill their air sacs with air within minutes and their lungs stay inflated. Patrick Kennedy died because he was born too early and his lungs were not mature enough. His death in 1963 made it a pivotal year for the field of Neonatology and energized researchers to find a cure for Hyaline Membrane Disease or the "immature lung disease".

Academic centers in the US started conducting clinical studies on many new treatments for premature babies. Physicians learnt how to modulate heat, oxygen and nutrition for these tiny babies. But other than oxygen there was not much else they could provide for the immature lungs. Then in 1971, George Gregory, an anesthesiologist at the University of California San Francisco developed a simple method by which he provided a constant distending pressure with a face mask to these premature babies and kept the air sacs in their lungs open. This strategy called CPAP saved the lives of many premature babies before mechanical ventilators were developed. Today, CPAP is saving the lives of many patients with COVID lung disease.

But why do the air sacs of premature lungs collapse? How do they stay open in adult lungs? Two scientists, John Clements and Richard Pattle, working separately in the US and UK, respectively, identified a substance from adult lungs that has a soap-like quality. Just as air bubbles in plain water collapse right away but stay stable in soapy water, the presence of this soap-like material inside the air sacs of mature lungs keeps the air sacs open and prevents them from collapsing. Dr Clements characterized this substance and called it Surfactant. Some years later, Dr Mary Ellen Avery at Harvard identified that premature baby lungs lacked this substance.

With the discovery of surfactant, immediately scientists and clinicians around the world wanted to find a way to give surfactant to premature babies. Dr. Clements started to synthesize an artificial surfactant. Right in the middle of this exciting time, in 1980, I came from India and joined Dr. Clements, Dr. Gregory and other giants in Neonatology at the University of California San Francisco. I learnt a lot from all of them and to this day Dr Clements remains one of my mentors.

So, in 1986, as I lay in the hospital feeling my labor contractions progress rapidly, with the birth of my premature baby very imminent, I wondered, “Should I call and ask Dr. Clements for his artificial surfactant for my baby?” But I knew he had not perfected it as yet. But my colleague at UCLA was collaborating with a scientist in Japan, who had extracted the surfactant from lungs of cows from the slaughter house. My colleague was testing this cow surfactant in premature lambs, since they developed a lung disease similar to premature babies.

I called him from my hospital bed. “Is there any way we could use the cow surfactant for my baby, in case he needs it?, “ I asked. “Usha,“ he said, “I don’t think so. We have not even started clinical trials in babies with any surfactant preparation! I don’t know if this cow surfactant would be safe to use it in your baby. And besides,” he said, “ it would be absolutely illegal to use it without FDA approval.”

“But please,” I persisted, “Can you tell me if it works in your premature lambs? Does it help their lungs stay open?”

“It does seem to be working,“ he confessed.

“Oh Please, please, please,” I begged. “Can you bring it to the hospital if my baby needs it?”

A day later, on June 7, 1987, my son Benjamin was born. He was born 7 weeks too early and very quickly developed severe lung disease, just like Patrick Kennedy, 24 years earlier. The doctors attached him to a mechanical ventilator and gave him pure oxygen but he just could not get enough oxygen into his blood. He remained blue. His lungs had no air in them and on Xray his lungs looked solid like a liver. My colleague, upon hearing how sick my son was, quickly sent his research associate with the cow surfactant to the hospital.

All the physicians and nurses in the neonatal intensive unit had to be sworn to secrecy as we were about to commit a crime. The atmosphere was filled with tension, excitement and trepidation. With his father Jeff Sugar and a family friend George Franco, another neonatologist, by his side, my son Benjamin Sugar got the cow surfactant solution poured into his lungs through his breathing tube. Dramatically, within minutes, his color improved. He required less and less oxygen over the next few hours and 12 hours after birth, he was detached from the ventilator and was placed in an incubator, to breath room air by himself. It took another two and a half years before Dr Clements’ artificial surfactant was approved by the FDA for clinical use in October 1989, and yet another year, for the cow surfactant to be modified and marketed by Abbott Laboratories.

The National Institutes of Health claims the discovery and development of surfactant therapy for premature infants as one of their landmark and most impactful contributions to science and medicine. Today with surfactant therapy and advances in neonatology, babies less than a pound at birth are surviving. But a large number of these tiny babies survive with severe brain and lung damage.

So now I come to my question, “How small is too small?” Where do we draw the line? The proponents of the utilization of the scientific advances of neonatal intensive care say that it has led to the survival of many babies who would not have survived otherwise and without a significant

increase in the number of handicapped children. The opponents say that neonatal intensive care is an example of medicine out of control—that it is the inappropriate use of technology by health care professionals playing God and who are out of touch with the sufferings of the families. They say that the benefits of survival are far outweighed by the burden of babies who survive with many long term disabilities.

The American Academy of Pediatrics together with the American College of Obstetrics and Gynecology defined a fetus as viable when it is mature enough to survive for at least the first month of life with all the clinical support that is available. And a viable fetus becomes a patient with their own rights as soon as a pregnant woman is introduced to obstetric care. A full term baby is born after 40 weeks of gestation. Currently it is accepted that all fetuses born before 22 weeks of gestation are non-viable and those born after 24 weeks of gestation or 5 and a half months of gestation are viable. Fetuses between 22-24 weeks of gestation fall in the grey zone.

How do we decide which tiny baby we should do everything for? Is it sufficient that we assess only survival potential? And if the criterion of survival is applied, is it sufficient that one baby survives? Or should it be 10%? Or 20%? What should it be? Currently, in the US a greater than 50% chance of survival is being used as an important criteria. And what about the potential for surviving with severe disabilities? How does that factor in our decision making? And if we consider residual disability as a criterion, what should be used, brain injury or lung injury, or multiple organ injury? How disabled does a child have to be after surviving to be defined as non-viable at birth? Such questions are very difficult to answer. In the US lawsuits against physicians for wrongful death have been won if the fetus had statistically a greater than 50% chance of survival but died due to presumed neglect on the part of the caregivers. On the other hand, parents have sued for wrongful life and won when physicians have cared for these very tiny babies and they have survived with disabilities.

The treatment of extremely premature babies always comes under fire because of the specter of babies surviving with disabilities. But this consideration does not seem to come into

play for other patient groups. In one study a panel of students was asked whether they would treat very tiny premature babies, or full term babies born with a severe congenital defects, or one year old infants with severe meningitis or 50 year old adults with injuries from a car accident. They were told that the outcomes were going to similar for all the four groups of patients i.e. They all had a 50% chance of survival and of those who survived 25% would have severe disabilities and 25% would have mild disabilities. Yet, only 35% of the students wanted to treat the premature babies compared to 52% who wanted to treat the full term babies with congenital malformations, 58% who wanted to treat the adults with injuries from a car accident and 74% who wanted to treat the infants with meningitis.

This lack of enthusiasm for treating the premature baby is the reason why guidelines for their care are essential. With advances in technology in medicine, the edge of viability keeps shifting to more and more immature babies and so we need to reassess these guidelines continually.

When I was at UCLA, one of my patients was an extremely tiny baby who weighed less than a pound at birth. Every day in the neonatal intensive care unit, without fail, he had one or two setbacks. His parents, together with their large extended family, came every day to listen to me explain what each set back meant and what we were doing to do help their son Samuel. They were always grateful and wanted us to do everything we could for him. So we kept adding a new intervention for each new complication he developed and he responded and stayed alive.

One day, when he was a month old, his heart stopped. We jumped into action and started pumping his heart. We added one then two and then three drugs to keep his heart going. His kidneys started to fail. His toes and then his feet started to turn black as he was not getting enough blood to his lower body. I called an emergency meeting of all his caregivers and his parents. This time I knew I had to tell them that I would have to stop all treatment. “All of Samuel’s organs are failing,” I told his parents. “I am just continuing his suffering by keeping him alive. I need to let him go. I need to withdraw all support.” Without hesitation, his parents pleaded,

“Please doctor, as long as Samuel is fighting for his life, please go on helping him”. And so I did. I doubt that any medical center in the US would have continued providing care under these circumstances. I did it because I was sure he would die within hours. But he did not. He survived. He went home after spending 8 more months in the hospital, still requiring oxygen and still being fed with a tube.

Four years later, at our annual party for all the graduates from our intensive care unit, a small, under-grown boy came tripping into the room laughing and clapping his hands. He was followed by his proud smiling parents and his large extended family. He did not have any speech. He raced from one child to the other in the room, smiling at them and looking back each time happily at his parents. He was full of life. He lit up the room. He was Samuel.