12-2020

Technology Aiding in Neonatal Lung Developmental Care

Megan Kirk

Technology Aiding in Neonatal Lung Developmental Care

By

Megan Elisa Kirk

Mentor: Dr. Hugh Blanton

Readers: Dr. Marko Kostic & Dr. Joseph Shrestha

Honors-in-Discipline Senior Thesis

Biomedical Engineering Technology

Abstract

In this paper, old as well as new technological findings to decrease premature infant mortality are reviewed. This paper discusses fetal development throughout pregnancy from conception to full-term status as well as fetal lung development specifically from conception until full-term status. Several ideas to rapidly develop and mature fetal lungs are discussed such as mothers ingesting artificial surfactant supplements, either independently or coupled with antenatal corticosteroids, as well as intra-amniotic instillation prior to 28 weeks gestational. Drawbacks regarding these two are mentioned as well such as the fetus's lungs not being mature enough to use the artificial surfactant leading into the idea of researching ways to rapidly develop fetal lungs, either week-by-week or stage-by-stage. Lastly, if the baby is born pre-maturely and is severely underdeveloped, research is currently being done on an artificial womb that the baby can be placed in to simulate a uterus where the fetus can develop on a normal timeline as he or she would in the mother's womb.

Acknowledgements

I would like to thank several people for helping me complete this undergraduate thesis. I would like to thank Dr. Marko Kostic for helping me start my thesis as well as guide and proof my paper along the way. I would like to thank Dr. Hugh Blanton for keeping me true with deadlines as well as proofing my paper. Lastly, I would like to thank Dr. Joseph Shrestha for proofing my thesis. Thank you all for being such an encouragement along my journey.

Table of Contents

Appendix

List of Figures

List of Tables

Introduction

Babies are the future of the world, but is the healthcare system doing all they can do to ensure these babies have the best future ahead of them? What about premature babies? While premature babies get extra attention due to being born before their gestational maturation stage, what can be done to possibly prevent premature birth or at least ensure a faster recovery time for this new infant so they do not have to spend the first few months in the Neonatal Intensive Care Unit, or NICU? This is not only a difficult road for the infant as they are connected to life-sustaining machines for weeks, but it also presents an also an enormous stress on the infant's family. Newborns crave the touch, smell, and bonding time with their parents, but the parents also crave this for their newborn baby. Being without this intimate bonding moment can often lead to stress for both parties, as along with delayed mental and physical development early-on as well as later in life (Flacking et al, 2012). With this being said, how can the healthcare system ensure premature babies are supported and healthy enough at the time of their birth to decrease their overall stay in the NICU after their birth? Furthermore, how can mortality rate be decreased among babies born prematurely, specifically at 24 weeks or younger? Technology is always evolving and could be a significant benefactor in detecting, as well as accelerating lung development in utero to result in a shorter hospital stay after a premature birth. This thesis will attempt to provide a greater insight into technologies currently being used to aid in these situations, and how can they be improved for better, quicker results.

Background

A fetus is considered to be full term at 39 weeks gestational (Know Your Terms, 2019). However, fetuses, or babies, are not always so compliant to this rule. Some babies want to meet their parents sooner, but this sooner-than-expected visit comes with a price. Babies are not considered “viable” until they are about 24 weeks gestational (When Is It Safe to Deliver Your Baby, n.d.). In fact, babies born before 24 weeks usually have less than a 50 percent chance of survival (When Is It Safe to Deliver Your Baby, n.d.). As weeks go on, the fetus matures more and more, and survival rates continue to rise as well. One of the most imperative elements of life is the act of breathing. This can be very difficult for babies who are born pre-term, as their lungs do not fully develop enough to work independently until later in the gestational phase. In fact, at birth, the lungs are still not fully developed; they continue to grow until 20 to 23 years of age (Hill, 2020). Table 1 provides a more in depth view of typical fetal development week to week until birth.

Fetal Development by Week

1st Trimester	Weeks 1 & 2	Getting Ready - Surprise! You are not actually pregnant during this time.
	Week 3	Fertilization - The sperm and egg unite to form a zygote.
	Week 4	Implantation - The zygote travels down to the uterus and begins dividing into a cluster of cells, called a blastocyte, and burrows into the uterine lining, or endometrium.
	Week 5	Hormone Levels Increase - Human chorionic gonadotropin, or HCG, levels are increased, and the embryo is now made of 3 layers.
	Week 6	Neural Tube Closes - The neural tube that runs along the baby's back is closing, the heart begins to form and beat, other organs also begin to form, and the arms begin to sprout.
	Week 7	Baby's Head Develops - The baby's brain and face begin to take shape and grow, and the legs begin to sprout.
	Week 8	Baby's Nose Forms - During this week, the baby actually begins to look like a baby as its facial features begin to form. Its fingers are also growing!
	Week 9	Baby's Toes Appear - The baby's arms are growing, the elbows have formed. The baby's toes are now visible. The head is large, but the chin is still underdeveloped.
	Week 10	Baby's Elbows Bend - The baby's head becomes more round, its elbows, fingers, and toes begin to wiggle, and the umbilical cord is clearly visible.
	Week 11	Baby's Genitals Develop - The baby is officially described as a fetus! The body begins to grow longer, and the genitals begin to form to identify the baby's sex.
2nd Trimester	Week 12	Baby's Fingernails Form - The baby's fingernails begin to grow, he or she has a more developed facial profile, and the intestines of the baby are in the abdomen.
	Week 13	Urine Forms - The baby begins to form urine and expel it into the amniotic fluid. The baby's bones are beginning to harden, especially the skull and long bones.
	Week 14	Baby's Sex Becomes Apparent - You may now be able to tell your baby's sex, but don't worry if you can't. It will become more apparent in the following weeks. The baby is forming red blood cells in the spleen.
	Week 15	Baby's Scalp Pattern Develops - The baby is growing rapidly. The baby's hair pattern is developing, and his or her bones are continuing to develop.
	Week 16	Baby's Eyes Move - The ears have almost completely formed, the eyes move slowly, and the skin is getting thicker. The arms and legs may move but not with enough force

		to be felt by the mother.
	Week 17	Baby's Toenails Develop - The baby's toenails are beginning to form, and the baby is becoming more active.
	Week 18	Baby Begins to Hear - The baby may now be able to hear sounds, the eyes are beginning to face forward, and the digestive system is now working.
	Week 19	Baby Develops Protective Coating - The baby is being coated in a greasy, cheese-like coating called vernix caseosa to protect the baby's delicate skin from abrasions, chapping, and hardening.
	Week 20	Halfway Point - By now, the mother can feel the baby's movements, the baby is regularly sleeping and waking, and he or she may even be awakened by loud noises.
	Week 21	Baby Can Suck His or Her Thumb - The baby is covered in fine hair to keep the vernix caseosa on the surface of the skin. The baby's suckling reflex is developing.
	Week 22	Baby's Hair Becomes Visible - The baby's eyebrows and hair are becoming visible. Brown fat is also forming as a source of heat.
	Week 23	Fingerprints and Footprints Form - The baby's eye movements become more rapid, ridges are forming on the baby's hands and feet that will eventually become prints, and the baby may also begin hiccupping.
	Week 24	Baby's Skin is Wrinkled - The baby's skin becomes wrinkled. The skin is translucent and may be a pink/red color due to visible blood in the capillaries.
	Week 25	Baby Responds to Others' Voices - The baby may be able to respond to familiar sounds such as the sound of the mother or father's voice.
	Week 26	Baby's Lungs Develop - The baby's lungs are beginning to produce surfactant, a substance that allows the air sacs in the lungs to inflate and not stick together once deflated.
	Week 27	2nd Trimester Ends - The baby's nervous system is continuing to mature. The baby is also gaining fat, making the skin appear smoother.
3rd Trimester	Week 28	Baby's Eyes Partially Open - The baby's eyes can partially open, and his or her eyelashes have formed. The central nervous system can direct rhythmic breathing movements and control body temperature.
	Week 29	Baby Kicks and Stretches - The baby can kick, stretch, and make grasping movements.
	Week 30	Baby's Hair Grows - The baby can open his or her eyes wide, the baby may have a headful of hair at this time, and red blood cells are forming in the baby's bone marrow.
	Week 31	Baby's Rapid Weight Gain Begins - Now that the baby has completed the majority of his or her development, it is time for the baby to quickly gain weight.
	Week 32	Baby Practices Breathing - The baby begins to lose the fine hair that was clinging to the protective coating, the baby's toenails may be visible, and the baby begins to practice breathing.
	Week 33	Baby Detects Light - The baby's pupils may begin changing size when stimulated by light. The baby's bones are hardening, but the skull remains soft so as to fit through the birth canal.
	Week 34	Baby's Fingernails Grow - The baby's fingernails have grown so much that they should reach his or her fingertips.
	Week 35	Baby's Skin is Smooth - The baby's skin continues to smooth out and may appear chubby.
	Week 36	Baby Takes Up Most of the Amniotic Sac - The space inside the uterus is becoming cramped for the baby, but the mother should still feel small movements as the baby wiggles, rolls, and stretches.
	Week 37	Baby Might Turn Head Down - The baby should have a firm grasp. Also, to prepare for birth, the baby's head may turn down and begin descending into the pelvic cavity.
	Week 38	Baby's Toenails Grow - The baby's toenails now reach the end of his or her toes. The baby has also shed most of his or her fine hair.
	Week 39	Baby's Chest is Prominent - The baby's chest is becoming more apparent, and he or she is gaining more fat to maintain heat after birth.

	Week 40	Mother's Due Date Arrives - The baby should be fully developed and prepared to make his or her entry any day.

Table 1. The above table shows the weekly gestational fetal development from 2 weeks prior to conception to full term (Mayo Clinic Staff, 2020).

Each progressing week in a fetus's maturation and growth is very critical and important. Critical fetal development starts as early as five weeks. At this time, the embryo begins developing its major system and structures (Fetal Development, 2020). From weeks six to seven, the embryo begins to form limbs, its brain forms into five separate sections, eyes and ears as well as tissues that will eventually form bones are developing, and the embryo's heart begins beating regularly (Fetal Development, 2020). At week eight, the embryo's arms, hands, legs, and feet continue forming and growing; the brain also continues growing, and the lungs begin to form (Fetal Development, 2020). By week nine, all of the embryo's major organs have begun growing (Fetal Development, 2020). At week 10, the baby is no longer considered an embryo, but instead, is considered a fetus from this moment until birth (Fetal Development, 2020). From weeks 11 to 14, the fetus continues defining its structures (Fetal Development, 2020). Weeks 15 to 18 are when the fetus begins to move around and stretch in utero (Fetal Development, 2020). This movement continues and intensities into week 22. During weeks 23 to 25, the fetus begins to form the lower airways of its lungs (Fetal Development, 2020). During week 26, air sacs in the lungs begin to form, but the lungs are still not supportive enough to ensure survival without help (Fetal Development, 2020). During weeks 27 to 30, the fetus's respiratory system begins to produce surfactant (Fetal Development, 2020). The Merriam-Webster Dictionary defines surfactant as "a surface-active substance" (Merriam-Webster, n.d.). Surfactant is indeed a surface-active substance within the lungs as it helps reduce surface tension at the air-liquid interface of the alveoli, or air sacs, within the lung to prevent collapsing at the end of exhalation (Nkadi et al, 2009). During weeks 31 to 34, the fetus's lungs still are not fully matured (Fetal

Development, 2020). Between weeks 35 to 37, the fetus's blood vessels and bones are fully formed (Fetal Development, 2020). From week 38 until birth, the fetus is considered full term, fully developed, and due any day (Fetal Development, 2020). While this goes into detail of the whole developmental process, lung development is not explicitly explained.

Biweekly Lung Development in Utero

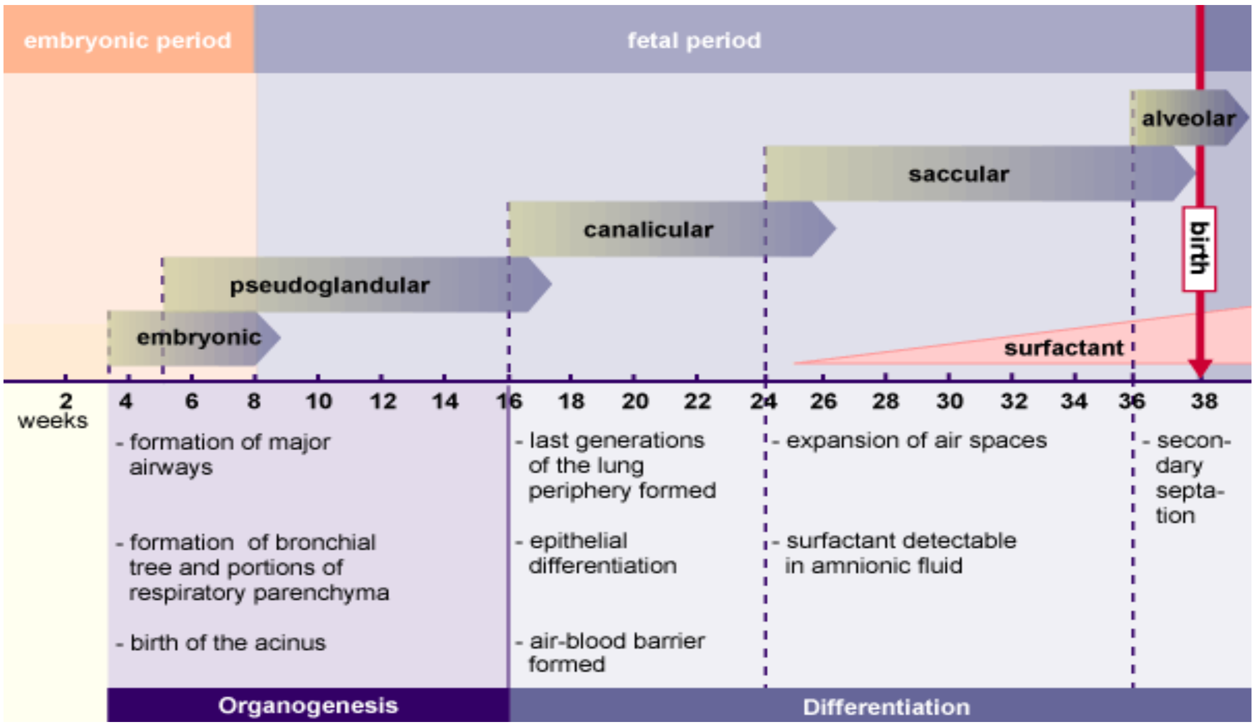

Figure 1. The figure above shows the biweekly development of the lungs from conception to full term.

From Figure 1, the timeline of which the lungs develop can better understood. From about three and a half weeks to 16 weeks, it is clear that the fetus forms major airways, the bronchial tree, portions of the respiratory parenchyma, and acinus. The parenchyma includes the gas-exchanging portion (Parenchyma, n.d.). The acinus is the smallest unit of lung tissue and consists of a terminal bronchiole and the lung parenchyma that will eventually form from it (Acinus, 2011). This stage includes the embryonic and pseudoglandular periods, and is the organogenesis portion of lung development. At 16 weeks, the organogenesis portion of lung development is complete, and the fetus enters into the differentiation portion. From 16 weeks to

24 weeks, including the termination of the pseudoglandular period and the bulk of the canalicular stage, the lung periphery is formed, the epithelial cells in the lungs start to differentiate and take on new jobs, and the air-blood barrier is formed. From 24 weeks to 36 weeks, or the termination of the canalicular period and the bulk of the saccular period, the air spaces or sacs of the lungs begin to expand as the fetus practices breathing and the first traces of surfactant are detected. Surfactant is first detected around 25 weeks and the amounts increase as the fetus progresses gestationally. Lastly, from 36 weeks to full term or birth, the fetus undergoes the termination of the saccular period as well as the full alveolar period where secondary septation occurs, meaning the alveoli in the fetus's lungs will separate and prepare for breathing air after birth. This is the completion of the differentiation portion of lung development.

As described earlier, the lungs are still not fully mature even at week 34. What happens when these babies are born prematurely? How does this premature birth affect further lung development out of utero and into the early stages of life? How are the lungs artificially matured in this setting? These are all very relevant and significant questions that contribute to learning more about gestational lung development and how researchers, doctors, and technologists can work to overcome and more effectively treat these infants so as to reduce overall time spent in the NICU. Seeing that surfactant is not detected in amniotic fluid until 25 weeks gestational, it is not a surprise that if the fetus is delivered around this time, the baby would have a difficult journey as they are not able to breathe on their own, or at least not efficiently, not only as an infant but also into their childhood or even adult life. So, what is the current treatment for premature babies with underdeveloped lungs? Because the lungs are underdeveloped, the babies' bodies are not able to deliver an adequate amount of oxygen to all of their organs and tissues. To treat this, it is common for the infant to receive oxygen therapy, or even a ventilator and medication (Healthwise Staff, 2017). This treatment allows the premature baby to absorb oxygen and ultimately breathe (Healthwise Staff, 2017). Medications given to premature babies often include diuretics or steroids to stimulate lung function, albuterol to aid in symptom relief, etc. (The Children's Hospital of Philadelphia, 2014). One of the main issues with premature baby lungs is the lack of surfactant. Premature baby's' lungs are typically treated with surfactant shortly after birth, and the baby's' oxygen-blood saturation levels normally increase almost immediately or within minutes (Healthwise Staff, 2017). The babies are treated with this surfactant intratracheally (List of Lung Surfactants, n.d.). Physicians can use several different types of surfactant. "In the US, artificial surfactant used for surfactant replacement therapy is extracted from the lung of a cow or a pig" (Mandile, 2018). Curosurf, generically known as poractant, chemically known as Poractant alfa [BAN], is a type of surfactant extracted from porcine lungs (Poractant alfa [BAN], n.d.). Infasurf, generically known as calfactant, is a type of surfactant extracted from bovine lungs (Bloom, B. T., et al, 1997). Survanta, generically known as beractant, is also extracted from bovine lungs. Surfaxin, generically known as lucinactant, is a synthetic substitution type of surfactant (Szydlo & Klemm, 2015). Another artificial surfactant is Exosurf, but it is no longer available (Palca, 2015). All of these different types of artificial surfactants aim to accomplish the same goal of helping the baby breathe. To accelerate lung development while in utero, some mothers choose to go through several rounds of corticosteroid injections resulting in rapidly matured lungs for the fetus (Healthwise Staff, 2017). "In the presence of preterm premature rupture of the membranes, antenatal corticosteroid therapy reduces the frequency of respiratory distress syndrome, intraventricular hemorrhage, and neonatal death, although to a lesser extent than with intact membranes" (Avery, et al, 1994). This means that in the case of a membrane such as the amniotic sac rupturing prior to full-term pregnancy status, these corticosteroids give the baby a better chance of not going into respiratory distress due to underdeveloped lungs. The mother can also be administered these steroids while the fetus is still in utero, but the effect on maturing the fetus's lungs without a ruptured membrane, like the amniotic sac, is less extensive. Avery, *et al* goes on to say that "antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality," (1994). Avery, *et al* includes the following legends and table, Table 2, to show the recommendations of each case the corticosteroids should or should not be administered (1994).

Evidence for Efficacy of Corticosteroids and Strength of Recommendation According to Delivery Interval, Gestational Age, Status of membranes, and Neonatal Outcome

	Quality of Evidence for Benefit	**Strength of Recommendation**
Interval from Treatment to Delivery		
<24 hours	I	B
24 hours to 7 days	I	A
>7 days	I	C
Gestational Age		
Delivery at 24-28 weeks	I	A
Delivery at 29-34 weeks	I	A
Delivery at >34 weeks	I	C
Preterm Premature Rupture of Membranes	I	B
Neonatal Outcomes		
Mortality	I	A
Respiratory distress syndrome	I	A
Intraventricular hemorrhage	I	A

Table 2 Legend 1: Quality of Evidence

I: Evidence obtained from at least one properly designed randomized controlled trial.
II-1: Evidence obtained from well-designed controlled trials without randomization.

II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940's) could also be regarded as this type of evidence.
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Table 2 Legend 2: Strength of Recommendation Regarding Corticosteroid Administration

A: There is good evidence to support use.
B: There is fair evidence to support use.
C: There is inadequate evidence to argue for or against use.
D: There is fair evidence to avoid use.
E: There is good evidence to avoid use.

Table 2. The above table and legends reviews the evidence for efficiency and the strength of recommendation to if corticosteroids should be administered (Avery, et al, 1994).

While studies are still being conducted and this method seems to be safe and effectual to give to mothers while in utero, it is not encouraged to have a premature infant receive several rounds of the corticosteroids directly as this has led to several ongoing issues in later years such as neurological damage, damage and bleeding to the gastrointestinal tract, blood sugar problems, which may lead to diabetes, and high blood pressure (Healthwise Staff, 2017). Because the monitoring and testing are so continuous and ongoing, the baby will be placed in an incubator in the NICU so the staff can keep a close eye on the baby's vital signs parameters to see that they are improving. The incubator also keeps the baby warm so they are able to maintain core body temperature. Once the baby can be held, skin-on-skin contact is commonly practiced for this same reason. If the baby's vitals do not improve within a certain amount of time, this could lead to a number of other issues such as chronic lung disease, or CLD, which is also known as bronchopulmonary dysplasia, or BPD (The Children's Hospital of Philadelphia, 2014). Medications may also be ordered to stimulate the lungs and strengthen breathing (Mayo Clinic Staff, 2017). In other words, current treatment for underdeveloped lungs in premature babies is the administration of surfactant and medication as well as a stay in the NICU to monitor the babies' overall health.

NICU Technology: Early Days and Current

How were premature infants treated in the early days, prior to current technologies? Pierre-Constant Budin was a French obstetrician who had a great impact on the health of pregnant women and their babies in the early 1900s (Payne, 2016). His career goal was to reduce infant mortality, and he did so by educating mothers on the importance of breastfeeding; when breastfeeding was not an option, he advised that sterilized cows milk be used to feed the infants to reduce infection and the spreading of bad bacteria (Payne, 2016). Budin also brought the term gavage to life. Gavage is basically feeding tubes that lead directly into the stomach. This innovation allowed physicians of the time to give proper nutrition to infants who were not able to eat on their own. Budin was the assistant to another French obstetrician, Etienne Stephane Tarnier (Payne, 2016). Tarnier recognized the need for incubators to keep the premature infants warm and allow them to grow and gain weight so he came up with the best solution he could given the era and the resources he had available. He came up with a wooden box with a glass lid and a hot water bottle inside (Payne, 2016). This innovation contributed to a 28 percent decrease in infant mortality within three years at the hospital where Dr. Tarnier worked (Payne, 2016). During this time, these special incubators were not accepted in hospitals due to its crude appearance (Payne, 2016). To encourage the incubator's popularity since it had such great potential for aiding premature babies, a student of Budin, Martin Couney, came up with an unconventional way to spread the word. In efforts to increase incubator popularity, Dr. Couney provided this treatment to infants free of charge (Payne, 2016). He would take these infants to local fairs and shows where he would charge onlookers 25 cents a piece to see the babies who were being kept alive by this new innovation to pay for the babies' treatments (Payne, 2016).

This practice, while unconventional, did its job of spreading the word because shortly after Dr. Couney died in 1950, American hospitals began allowing the use of incubators for the care of premature babies (Payne, 2016). "It was not until after World War II that hospitals began to create Special Care Baby Units, the precursors to modern NICUs," (Payne, 2016). Special Care Units for infants became a staple when doctors began to realize that "heat, humidity, and a steady supply of oxygen" lead to an increase in survival rate among infants (Payne, 2016). Initially, hospitals were hesitant to implement incubators due to the expense, restricted access, and lack of confirmation of its effectiveness, but the decreased mortality rate was too obvious to ignore. The original incubator was later amended and improved by Dr. Julian Hess at Reese Hospital in Chicago, Illinois when he not only was able to regulate heat and humidity, but also administer oxygen to the infants (Payne, 2016). "The following decade, incubators with clear plastic walls were introduced, allowing doctors and nurses to easily see and access the babies," (Payne, 2016).

Dr. Louis Gluck discovered that washing babies regularly lead to a decrease in infection among these infants; regardless of how clean the babies were, one of the biggest issues in spreading bacteria and infection among these infants was getting the staff and visitors to wash their hands before handling the children (Payne, 2016). "To this day, this remains one of the biggest threats in the NICU," (Payne, 2016). Gluck eventually redesigned the Special Care Nursery to have all the incubators in one room instead of sectioned off so it was easier for the doctors and nurses to easily access and manage the care of each infant (Payne, 2016). Gluck was also instrumental in the design of the L/S ratio test (also known as the Lecithin-Sphingomyelin ratio), which determines the maturity of infant's lungs (Payne, 2016). This, in turn, provides indications of infant's chances of developing certain respiratory diseases. Because of these accomplishments, Gluck is often hailed as the father of neonatology (Payne, 2016).

Until the 1970s, most of the emphasis was placed on devices, and family involvement was not much of a thought. In the 1970s, however, this all began to change (Payne, 2016). "The Newborn Individualized Developmental Care and Assessment Program was developed by Heidelise Als, which encouraged family involvement and individualized plans for each baby," (Payne, 2016). Once the program began, doctors learned family involvement dwindled down the amount of days the babies required ventilators (Payne, 2016). "Kangaroo care," or skin-to-skin contact became a very significant aspect in the babies' health due to the importance of the parent-child bond that aids in "bonding, stabilize the baby's breathing, heart rate and body temperature, and help the baby gain weight and grow," (Payne, 2016). Because of the bonding and how well the babies were responding, many hospitals initiated visiting hours so the families of the infant could come in and bond with them (Payne, 2016).

In the 1990s, as technology became more readily available, affordable, and understandable, the care for more high-risk babies became more attainable; babies born as early as 23 weeks gestational, and weighing as little as one pound were being able to be saved (Payne, 2016). As of earlier this year, survival rates are typically as following:

Average Likelihood of Infant Survival by Gestational Age

Gestational Age	Likelihood of Survival
22 weeks	0%
23 weeks	17%
24 weeks	39%
25 weeks	50%
26 weeks	80%
27 weeks	90%

28-31 weeks	90-95%
32-33 weeks	95%
34+ weeks	95-100%

Table 3. The above table indicates the chances of infant survival based on what gestational age they are born (Danielsson, 2020).

While this is fairly accurate, there are a couple of babies who may experience a miracle. For example, in Decatur, Georgia, on December 20, 2019, the youngest surviving premature baby was born at 21 weeks, 0 days gestational (Bilger, 2020). There are also a number of babies being born at 22 weeks gestational that are surviving. While it is still questionable how the children will do long term, they are currently living and thriving.

Technology has since improved and is continuously improving and also improving neonatal care. A NICU has a lot of equipment they use on a daily basis. A few machines used daily by staff on NICU babies include, but are not limited to heart or cardiorespiratory monitors, blood pressure monitors, thermometers, pulse oximeters, portable x-ray machines, CT scanners, MRI machines, endotracheal tubes (ET), respirators or mechanical ventilators, continuous positive airway pressure (CPAP) machines, and extracorporeal membrane oxygenation (ECMO) machines (Stanford Children's Health Staff, n.d.). All of these technologies, along with technologies that are currently being developed, can help further decrease premature infant mortality rate.

Significance

Why does this research need to be done? What is wrong with the current way things are being done? Babies are still being successfully saved as young as 21 and 22 weeks gestational. How will additional research better or advance the process of lung development in a quicker, more effective way? Will focusing solely on rapid lung development in utero be enough to deem more at risk babies viable and savable? How long will developing a new technology take? How much will research, design, and manufacturing cost? Is the healthcare system willing to do experimental trials on pregnant women and their babies? These are all relevant questions that are currently up in the air as research is being done to look for answers to solve this issue of losing premature babies in hopes to decrease infant mortality rate.

This research needs to be done to save more premature lives and decrease mortality rates. While the current way things are being done, using surfactant as well as medication to stabilize and aid the infant before they can breathe on their own, is efficient, there is always room for improvement. Researchers and healthcare workers need to be looking at how the lungs are developed in utero and the process and stages the respiratory system goes through in order to stabilize the lungs to a point where they can operate on their own at an earlier gestational age. Once this process is known and understood, research can be done to look into treating all fetuses while still in utero as a precautionary measure in case the fetus was to be born before they reach full-term. By designing and researching new, innovative ideas to aid in enhancing surfactant production levels while still in utero, the amount of lung related complications the premature infant might encounter can hopefully be eliminated, or at least minimized. This may also prove to decrease the premature mortality rate alongside finding new, creative ideas, as the main goal is to save as many lives as possible. If jumpstarting lung development in utero is not attainable, is there possibly a way to preserve the fetus outside the amniotic sac to allow the baby to fully develop without all of the complications? Whatever the future holds, not only will babies be saved, but this will also be saving parents from heartache and a long recovery road. Bringing a baby into the world should remain beautiful and intimate, instead of turning the mood into a gloomy, possibly worst day of your life moment.

Methods

How was this research conducted? The research done for this study really dove in to see what research had already been done, what ideas had been successful, and which have failed. Is there anything that past researchers have overlooked or missed? It studied what technology and medication were part of the current protocols, and while they work, research suggests the process could be sped up and be more effective. The research focused in on new and upcoming technologies that are still under development in order to more proficiently treat the still-developing lungs of premature babies. It looked at studies done to boost surfactant stimulation and secretion earlier than the normal 25 to 30 weeks gestational. It also looked at studies done after birth to boost the infant's respiratory system in a quicker manner than the current practice of supplying the infant with surfactant while the infant stays in an incubator in the NICU until they are considered to have strong enough lungs to be able to breathe independently. This research lastly looked at ways to preserve the fetus if it is born prematurely so they are able to continue developing as if they were still in the amniotic sac in the mother's uterus. The main goal of this study is to provide faster, successful care to premature infants born with underdeveloped lungs still needing aid to save the baby's life and decrease infant mortality at the time of birth.

Discussion

The main causes of mortality in premature infants revolve around issues with the heart and lungs. Drugs have been created to aid the mother in stopping preterm labor, but these drugs do not always work. What happens if the baby is still born prematurely? How much is really known about fetal development, and how can researchers learn more about, not just the fetal development timeline but also the processes in which each phase of development occurs? Can these processes be manipulated and the order of development be switched up? So far, this study has looked at what has been done in the past as well as current protocols, but can be done to better address the issue at hand? Research needs to be done to brainstorm new ideas that will aid in saving premature babies born way before term. Ideas may regard the baby while still in utero or after birth. One idea that needs to be tested is surfactant supplements for the mother to take while the baby is still in utero. Similar to the prenatal vitamins that pregnant women take to provide extra nourishment for themselves and the fetus, this type of supplement would target the fetus's lung developmental process and jumpstart the production of surfactant for the fetus before natural surfactant is produced around 25 weeks gestational. Another idea would be to administer surfactant to the fetus directly or add it to the amniotic fluid. Both of these ideas, if successful, would be a precautionary measure just in case the mother would happen to go into preterm labor. There is also current research being done regarding placing the baby in an artificial sac resembling the amniotic sac. The baby would stay in this sac until it was considered full-term. Then, the sac would be broken, and the baby's developmental progression would be assessed to determine further action. Overall, the healthcare system, physicians, and researchers are always looking for new advancements and technologies that are going to benefit billions of mothers, babies, and families all over the world.

A study that would need to be performed would be to evaluate what impact artificial surfactant supplements ingested by the mother might have on the fetus. What does surfactant actually consist of? "Lung surfactant is a complex with a unique phospholipid and protein composition," (Bernhard, 2016). The article goes on to say, "Surfactant comprises 80% phosphatidylcholine (PC), of which dipalmitoyl-PC, palmitoyl-myristoyl-PC and palmitoyl-palmitoleoyl-PC together are 75%. Anionic phosphatidylglycerol and cholesterol are about 10%

each, whereas surfactant proteins SP-A to -D comprise 2-5%," (Bernhard, 2016). Surfactant is "secreted by type II alveolar cells into the alveolar epithelial lining," (Chaiworapongsa, Hong, Hull, Romero, & Whitsett, 2008). While antenatal corticosteroids are administered to mothers at risk of pre-term labor between 23 and 26 weeks gestational to hasten fetal lung development between 28 to 34 weeks, there is no evidence to suggest that the steroids increase fetal lung development if administered prior to 23 weeks gestational (Wapner, 2013). The steroids are used to speed up the secretion of natural surfactant in the fetus, but if artificial surfactant is administered to the mother prior to 23 weeks, either independently or coupled with the antenatal corticosteroid, would this better prepare the fetus if it were to be born prematurely? Would the fetus even be far enough along in its lung developmental process for this to be beneficial? If the lungs are not sufficiently developed enough prior to 23 weeks for this to be beneficial, is there a way to stimulate lung development week-by week or even stage-by-stage, for example, embryonic, pseudoglandular, and canalicular? No studies are currently being conducted to answer these questions, but, in theory, it seems like it would be something that may provide favorable outcomes for the infant. If successful, this could be administered only to women who are at risk of going into pre-term labor or to every pregnant woman as a preventative measure.

In addition to the previous idea, another study that needs to be further investigated is injecting artificial surfactant into the amniotic sac in the mother's womb as a precaution in case the mother was to go into pre-term labor. The surfactant would be injected near the fetus's mouth and nostrils so as to enter the fetus's "airways" before it's birth (Abdel-Latif, Osborn, Challis, 2010). Preliminary animal and human studies have been conducted and deemed successful; however, no high-quality studies have since been conducted (Abdel-Latif, Osborn, Challis, 2010). Studies have been conducted to conclude that intra-amniotic instillation reduces respiratory distress syndrome, or RDS, among women who are 28 to 34 weeks pregnant, but studies on women who are earlier than 28 weeks have not been performed (Agarwal, Bathwal, Kriplani, Deorari, & Bhatla, 2016). As before, if this is tested and tried, initially, researchers need to know if the fetus's lungs are even capable of using surfactant before it is naturally made. If not, to reiterate, researchers could look into ways to stimulate lung development either week-by-week or stage-by-stage. Anything that can be done to rapidly develop fetal lungs will increase the fetus's chances of survival out of the womb.

One technological innovation that is still being studied and explored is an artificial womb, commonly referred to as a biobag (Adereyko, 2020). In theory, once the fetus is born prematurely, the baby would be placed in an artificial sac resembling the amniotic sac where the infant would be able to continue with the development until the sac is broken at, what would be considered, full-term (Regis College, 2020). The artificial amniotic fluid is continuously exchanged as to maintain and preserve the fluid filled lungs (Partridge, Davey, Hornick, et al, 2017). In 2017, Erika Engelhaupt wrote an article stating, "eight fetal lambs survived and grew inside an artificial womb for four weeks, the longest an animal has done so" (Engelhaupt, 2017). While the lamb was in the artificial womb, its organs, including the lungs, developed just as if it was in the mother's womb (Engelhaupt, 2017). The lambs grew into adulthood seemingly having no problems and have had normal development since birth (Engelhaupt, 2017). It is hard to gain a grasp on their mental state as there is no "intelligence test" for lambs, and this is concerning as researchers still question the effectiveness as they cannot understand how a human fetus would react (Engelhaupt, 2017). Even without knowing the mental drawbacks this method might have on human fetuses, the idea of placing a fetus in an artificial womb so it can develop normally up until full-term status is definitely something physicians should be able to get behind for the benefit of the child. The article goes on to say, "If the new device succeeds, the parents of a premature baby might someday peer into an incubator that looks a bit like an aquarium" (Engelhaupt, 2017). The baby would be placed in a clear, large bag filled with artificial amniotic fluid; the baby would "breathe" the artificial amniotic fluid just as they would in the mother's womb, and the umbilical cord would be hooked up to a machine that would supply oxygen and eradicate carbon dioxide (Engelhaupt, 2017). The main goal of the artificial womb, however, is not to "extend the limits of viability," but to "improve survival for extremely premature infants" (Engelhaupt, 2017). The fetus would be "delivered" from the artificial womb at about 28 weeks of typical gestation to lessen the risk of infection (Engelhaupt, 2017). The lungs would be developed sufficiently to breathe on their own at this point as well (Engelhaupt, 2017). More testing is still being done on animal subjects before researchers can move on to human testing, but researchers are hopeful to begin testing on humans in the next three to five years (Engelhaupt, 2017). A disadvantage of this method would be cardiac failure due to added stress on the fetus's heart due to the umbilical oxygen/carbon dioxide pump (Partridge, Davey, Hornick, et al, 2017). While this method would not necessarily cut down on overall time in the NICU, it would give the infant a better chance at proper development as well as not having any physical or mental deficits later on in life, such as cerebral palsy.

Conclusion

In summary, the goal is to save the lives of as many premature infants as possible. In addition, not only will these new innovation have the ability to save these babies' lives, but these innovations will also be guarding the babies' parents from the heartache of losing a child. This study looked into several different alternatives to the current practice of treating premature infants. It specifically investigated the surfactant supplements for the mother to take while still pregnant with the fetus, either independently or paired with antenatal corticosteroids. Additionally, the study assessed intra-amniotic instillation before 28 weeks gestational. Lastly, this study examined the artificial sac, or biobag, for premature babies to go into at the time of premature birth to simulate the environment of still being in the uterus so they could develop until they are considered full-term. Each of these ideas and innovations involve either rapidly developing fetal lungs or allowing the fetal lungs to mature at a normal pace, just outside the mother's body. They each have the goal of giving the baby the best chances of survival outside the womb. In conclusion, all lives matter and deserve the best chance at life, even the lives of babies that have not even entered the world yet. In doing this research, several ideas have been found that warrant further research that may eventually surpass the current practices in neonatology and save additional lives worldwide.

Bibliography

Abdel-Latif ME, Osborn DA, Challis D. (2010). Intra-amniotic surfactant for women at risk of preterm birth for preventing respiratory distress in newborns. Cochrane Database of Systematic Reviews, Issue 1. Art. No.: CD007916. DOI: 10.1002/14651858.CD007916.pub2

Acinus. (2011) Segen's Medical Dictionary. Retrieved from https://medical-dictionary.thefreedictionary.com/acinus

Adereyko, O. (2020, April 30). Artificial Womb for Humans: A Step Forward in Survival for Premature Babies. Retrieved from https://flo.health/pregnancy/pregnancy-health/fetal-development/artificial-womb-for-humans

Agarwal, N., Bathwal, S., Kriplani, A., Deorari, A., & Bhatla, N. (2016). Intra-amniotic I nstillation of surfactants for the prevention of neonatal respiratory distress syndrome following preterm delivery. *International Journal of Gynecology & Obstetrics,135*(2), 196-199. doi:10.1016/j.ijgo.2016.03.039

Avery, M. E., M.D., Ballard, P. L., M.D., Ph.D., Ballard, R. A., M.D., et al (1994, February 28-March 2). The National Institutes of Health Consensus Development Program. *The Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes-interim draft statement. NIH Consens Statement Online, 95*(12)2, 1-24. Retrieved from https://consensus.nih.gov/1994/1994AntenatalSteroidPerinatal095html.htm

Bernhard W. (2016). Lung surfactant: Function and composition in the context of development and respiratory physiology. *Annals of anatomy = Anatomischer Anzeiger : official organ of the Anatomische Gesellschaft*, *208*, 146–150. https://doi.org/10.1016/j.aanat.2016.08.003

Bilger, M. (2020, June 24). Born at 21 Weeks, Youngest Surviving Premature Baby in the World Now Heading Home. Retrieved from https://www.lifenews.com/2020/06/24/born-at-21-weeks-youngest-surviving-premature-baby-in-the-world-now-heading-home/

Bloom B. T., Kattwinkel J., Hall R. T., Delmore P. M., Egan E. A., Trout J. R., Malloy M. H., Brown D. R., Holzman I. R., Coghill C. H., Carlo W. A., Pramanik A. K., McCaffree M. A., Toubas P. L., Laudert S., Gratny L. L., Weatherstone K. B., Seguin J. H., Willett L. D., Gutcher G. R., Mueller D. H., Topper W. H. Comparison of Infasurf (calf lung surfactant extract) to Survanta (Beractant) in the treatment and prevention of respiratory distress syndrome. Pediatrics. 1997 Jul;100(1):31-8. doi: 10.1542/peds.100.1.31. PMID: 9200357.

Chaiworapongsa, T., Hong, J. S., Hull, W. M., Romero, R., & Whitsett, J. A. (2008). Amniotic fluid concentration of surfactant proteins in intra-amniotic infection. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the*

International Society of Perinatal Obstetricians, *21*(9), 663–670. https://doi.org/10.1080/14767050802215664

Danielsson, K. (2020, April 20). What Are the Odds of My Premature Baby Surviving? Retrieved from https://www.verywellfamily.com/premature-birth-and-viability-2371529 Medically reviewed by Meredith Shur, MD

Engelhaupt, E. (2017, April 25). Artificial Womb Could Offer New Hope for Premature Babies. Retrieved from https://www.nationalgeographic.com/news/2017/04/artificial-womb-lambs-premature-babies-health-science/

Fetal Development: MedlinePlus Medical Encyclopedia. (2020, April 9). Retrieved from https://medlineplus.gov/ency/article/002398.htm

Flacking, R., Lehtonen, L., Thomson, G., Axelin, A., Ahlqvist, S., Moran, V. H., Ewald, U., Dykes, F., & Separation and Closeness Experiences in the Neonatal Environment (SCENE) group (2012). Closeness and separation in neonatal intensive care. *Acta paediatrica (Oslo, Norway : 1992), 101*(10), 1032–1037. https://doi.org/10.1111/j.1651-2227.2012.02787.x

Healthwise Staff. (2017, May 4). Premature Infant: Treating Underdeveloped Lungs. Retrieved from https://wa.kaiserpermanente.org/kbase/topic.jhtml?docId=tn6342

Hill, M.A. (2020, May 5). Embryology. *Respiratory System Development*. Retrieved from https://embryology.med.unsw.edu.au/embryology/index.php/Respiratory_System_Development

Know Your Terms: Moms-to-be - NCMHEP. (2019, October 12). Retrieved from https://www.nichd.nih.gov/ncmhep/initiatives/know-your-terms/moms

List of Lung surfactants. (n.d.). Retrieved from https://www.drugs.com/drug-class/lung-surfactants.html

Mandile, O. (2017, April 30). Neonatal Respiratory Distress Syndrome and Its Treatment with Artificial Surfactant". *Embryo Project Encyclopedia.* Retrieved from https://embryo.asu.edu/pages/neonatal-respiratory-distress-syndrome-and-its-treatment-artificial-surfactant

Mayo Clinic Staff. (2017, December 21). Premature birth. Retrieved from https://www.mayoclinic.org/diseases-conditions/premature-birth/diagnosis-treatment/drc-20376736

Mayo Clinic Staff. (2020, June 30). Fetal development: What happens during the 1st trimester? Retrieved from https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/prenatal-care/art-20045302

Mayo Clinic Staff. (2020, June 30). Fetal development: What happens during the 2nd trimester? Retrieved from https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/fetal-development/art-20046151

Mayo Clinic Staff. (2020, June 30). Fetal development: What happens during the 3rd trimester? Retrieved from https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/fetal-development/art-20045997

Merriam-Webster. (n.d.). Surfactant. In *Merriam-Webster.com dictionary*. Retrieved May 5, 2020, from https://www.merriam-webster.com/dictionary/surfactant

Nkadi, P. O., Merritt, T. A., & Pillers, D. A. (2009). An overview of pulmonary surfactant in the neonate: genetics, metabolism, and the role of surfactant in health and disease. *Molecular genetics and metabolism, 97*(2), 95–101. https://doi.org/10.1016/j.ymgme.2009.01.015

Palca, J. (2015, August 03). How A Scientist's Slick Discovery Helped Save Preemies' Lives. Retrieved from https://www.npr.org/sections/health-shots/2015/08/03/422620170/how-a-scientists-slick-discovery-helped-save-preemies-lives

Parenchyma. (n.d.) Farlex Partner Medical Dictionary. (2012). Retrieved October 11 2020 from https://medical-dictionary.thefreedictionary.com/parenchyma

Partridge, E., Davey, M., Hornick, M. *et al.* An extra-uterine system to physiologically support the extreme premature lamb. *Nat Commun* **8**, 15112 (2017). https://doi.org/10.1038/ncomms15112

Payne, E. (2016, January 5). A Brief History of Advances in Neonatal Care. Retrieved from https://www.nicuawareness.org/blog/a-brief-history-of-advances-in-neonatal-care

Polin, R. A., & Carlo, W. A. (2013). Surfactant Replacement Therapy for Preterm and Term Neonates With Respiratory Distress. *Pediatrics,133*(1), 156-163. doi:10.1542/peds.2013-3443

Poractant alfa [BAN]. (n.d.). Retrieved from https://chem.nlm.nih.gov/chemidplus/rn/129069-19-8

Regis College. (2020, May 15). 5 Advances in Medical Technology for Neonatal Nurses: Regis. Retrieved from https://online.regiscollege.edu/blog/5-advances-nicu-equipment-medical-technology-neonatal-nurses/#:~:text= 5 Advances in NICU Equipment and Medical,A Neonatal Intensive... 4 Sources:. More

Stanford Children's Health Staff. (n.d.). Equipment That is Used in the NICU. Retrieved from https://www.stanfordchildrens.org/en/topic/default?id=equipment-that-is-used-in-the-nicu-90-P02358

Szydlo, R. T., R.Ph., M.B.A., R.A.C., & Klemm, K., Pharm.D., R.A.C. (2015, March 3). NDA 021746 [Letter written March 3, 2015 to Dr. Lorraine J. Lucas]. Retrieved from https://www.fda.gov/media/91041/download

The Children's Hospital of Philadelphia. (2014, August 24). Infant Chronic Lung Disease. Retrieved from https://www.chop.edu/conditions-diseases/infant-chronic-lung-disease

Wapner R. J. (2013). Antenatal corticosteroids for periviable birth. *Seminars in perinatology*, *37*(6), 410–413. https://doi.org/10.1053/j.semperi.2013.06.024

When Is It Safe to Deliver Your Baby? (n.d.). Retrieved from https://healthcare.utah.edu/womenshealth/pregnancy-birth/preterm-birth/when-is-it-safe-to-deliver.php