Background, Physiology and Ethics of Artificial Placentas

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ABSTRACT

Preterm birth, referring to when a baby is born before 37 weeks of pregnancy, is the leading cause of death in young children and is associated with many complications for the individuals who survive. The current intensive care treatment for preterm infants involves many pieces of medical equipment, physiological stressors, and ethical dilemmas. Many of these issues could be addressed with the use of a fluid-filled sac that mimics the placental environment: an artificial placenta (AP).

This paper explores the history of how animal models have been used to test AP devices. Further, this article highlights the physiological stress that preterm infants experience when being removed from a placental environment and surrounded by life-saving medical equipment. The paper also explores potential future uses of and procedures involving APs. It concludes with an exploration of AP bioethical considerations through autonomy, beneficence, nonmaleficence, and justice.

In summary, this paper attempts to compile an overview of AP technology by exploring the background, physiology, and ethical considerations involved in this technology.

Introduction

The concept of an artificial placenta has been on fiction writers' minds for over 50 years. The novel Brave New World by Aldous Huxley was published in 1932 and details a fictional society that uses an artificial birthing process. In the book, surgically removed human eggs are placed into test tubes, fertilized with sperm, and incubated to produce fetuses. Although artificially incubated fetal development is so far only realized in science fiction literature, real-life AP fetal development has potential. A human egg must be fertilized with sperm and implanted into the uterus for development (Vander et al., 1998). This fertilized egg then divides and multiplies, creating a blastocyst with a placental-like outer layer (trophectoderm) surrounding the embryonic cells (inner cell mass) (Vander et al., 1998). These embryonic cells further divide and develop into a fetus, which becomes an infant after birth. The placenta is a versatile, fluid-filled organ that develops in the uterus during pregnancy and is essential for

facilitating nutrient and gas exchange between the mother and the fetus (Kumpel et al., 2008). The placenta helps protect the fetus from the external environment. The primary purpose of an AP is to mimic the function of an endogenous placental environment. "Endogenous" refers to something originating within an organism, such as a human. A real AP would require a fluid-filled sac, made from either artificial materials or placental stem cells, that could contain a fetus through its development. The concept of an AP can include the housing of a fetus at any point during fetal development. The trophectoderm does not start to differentiate from the original cell mass until around the fifth day (Vander et al., 1998). A fluid device that helps maintain growth, whether the device contains a 5-day-old inner cell mass or a 36-week-old fetus, would be considered an AP.

An AP would have many functions, and equipment could differ widely depending on the AP's current use. Much of this paper will focus on the AP's primary function: to grow a fetus in an environment that could minimize the physiological stress experienced during preterm births. Preterm births, when delivery occurs after week 22 and before week 37 of pregnancy in humans, can cause health concerns, such as underdeveloped organs or low birth weights (Bird, 2017). Infants born at full term must undergo huge physiological stress due to the change in their external environment from liquid to air. Many organs, such as the lungs and heart, must quickly accommodate these changes. In a preterm infant with underdeveloped organs, this added stress must often be accommodated with the help of external medical devices, such as ventilators or pumps. The use of APs removes this initial stressor, because the preterm infant is transferred directly from the endogenous placenta to the AP. The warm, artificial, amniotic-fluid-filled environment then allows the fetus to develop further with minimized physiological stress. A small section of this paper will analyze how APs could be utilized for the development of blastocysts into full-term fetuses in an artificial environment. This

function may never be possible, as many unknown placental mechanisms, nutrients, and development stages must first be elucidated. If all of these fundamental placental obstacles are overcome, many societal and logistical aspects will also become barriers. Therefore, full-term AP fetal development is examined, but there is limited research to support it.

This paper will present a brief background on past and current AP research, explore APs' physiological basis, and examine the ethical considerations required for AP technology through the four basic healthcare ethics principles. These four principles include autonomy, beneficence, nonmaleficence, and justice.

Terms and Limitations

The word "fetus" will be used whenever a developing individual is contained in a fluid state. The word "infants" will be used when the individuals are in an air environment. "Full-term AP" denotes fetal development from the fifth day of blastocyst development to the end of the full-term. "Preterm AP" denotes the transfer of a fetus from the endogenous environment to an AP. This paper is not intended to be a complete review of all the literature on the topic of APs, but an examination of critical points and ethical considerations. Although medical techniques are discussed for human APs, many further advancements in the field would be required before any human experimental attempts would be permitted.

Background

The first documented research article containing the words "artificial placenta" was published in 1946 and mostly looked at mechanical oxygenation (Noer, 1946). Unno et al. (1993) performed a study that incubated premature goat fetuses in an extra-uterine sac with artificial amniotic fluid and vascular circulation. These goat fetuses were maintained in the sac for around 20 days. With breathing support, they survived for over a week outside of the AP system. Although this process is still in an infantile stage, the beginnings of real-life AP fetal

development were already occurring in the 1990s. Throughout the next 25 years, some experiments were conducted on fetal animals in an AP environment, but were sporadic (Bird, 2017).

A significant leap towards APs' development and use was presented in a 2017 study with incubated lambs. The Partridge et al. (2017) study used a pumpless oxygenator in an amniotic fluid-like circuit to incubate immature lambs. The researchers inserted thin tubes (cannulas) into the neck or umbilical vessels of each fetus to create a closed vascular circuit. The lambs were placed into sterile 'Biobags' filled with an electrolyte solution. These lambs were incubated for about a month, during which organ growth and maturation were observed. The umbilical vessels were determined to be the only sufficient physiological vasculature route for normal placental access. The Partridge et al. paper indicated that the best clinical target would be 23-to-25-week-old premature infants. The death and complication rate of this targeted age group could be significantly reduced with AP technology. More mature age groups would have to be further examined to determine if an AP could drastically improve outcomes.

In-vitro fertilization (IVF) is a pre-established procedure that would likely be required for development of the full-term AP process. IVF would likely have to be performed at the beginning of the full-term AP procedure to obtain an intact, developing embryo. IVF involves removing an egg from a female and sperm from a male; fertilization of the egg occurs in a glass dish (Wang & Sauer, 2006). This fertilized egg can then divide and is normally implanted into the uterus. This fertilized embryo can develop for up to five days in a fluid-filled dish (Wang & Sauer, 2006). The blastocyst contains a placenta-like structure and the embryo. At this stage, the blastocyst is typically implanted into the uterus, but could be implanted into an artificial uterine environment for continued growth. Another option would be separating this inner cell mass, which composes the future fetus, and transferring

it to an artificial pre-placental structure. However, this scenario could cause more disturbance and damage to the embryo than necessary. For full-term AP fetal development, the use of an extra-uterine environment may be more realistic.

Physiology

An AP can replicate the physiological requirements of an endogenous placenta to help premature fetuses develop. An average full-term gestation, the time the fetus spends in the womb, is around 40 weeks (Vander et al., 1998). However, a human fetus can be viable outside the womb as early as 22 weeks into gestation (Vander et al., 1998). In cases of premature delivery, many organ systems are immature. The fetus's main requirements from the mother are oxygen and nutrients, which are received from the placenta through the umbilical cord circulation (Vander et al., 1998). Recent studies have used the umbilical arteries and veins to connect to the AP equipment (Partridge et al., 2017). This equipment was connected for the purpose of delivering oxygen and nutrients (in place of the mother). The fetus was also placed in a warm synthetic amniotic fluid. This amniotic fluid protected the fetus from the external environment by surrounding it with liquid. Some nutrition uptake may also have occurred through this fluid. Most importantly, the amniotic fluid filled the fetus's airway and lungs to maintain the pressure required for normal fetal development. Respiratory failure is a common issue for premature infants, as they often have inadequate lung structure development. The lungs in a developing fetus are fluid-filled. Therefore, the sudden change to air-filled alveoli, branched lung structures that facilitate gas exchange, can be remarkably abrupt. The first breath after birth is known to be one of the hardest in life. If lung structures are not entirely developed, the lungs may not properly function or may create a significant struggle as premature infants try to breathe. This struggle is often alleviated by the use of a ventilator, a machine that artificially breathes for the patient.

The use of an AP should reduce the medical equipment required for premature infant care. The current medical equipment required when a preterm infant enters the Neonatal Intensive Care Unit (NICU) can include an incubator that regulates the temperature of the baby's environment; oxygen, temperature, and blood pressure monitors; intravenous catheters (IVs) or central lines for medication administration; feeding tubes; phototherapy lights; and ventilators (Bergon-Sendin et al., 2015). Many, if not all, of these medical devices are required to sustain the preterm infant's life. Many of these devices can also add to the stress experienced by the infant. Noises, movement, and technology poking or entering the infant's body are all huge potential stressors. After birth, the infant must physiologically accommodate an environment where they are surrounded by air and not fluid. The AP environment removes most, if not all, of these potential stressors. The fetus could continue developing in a fluid-filled climate, most noises would have a decreased volume from fluid protection, and there would be limited external or internal medical instruments directly attached to the fetus. An AP's setup would require an oxygenator; an amniotic fluid reservoir tank; and blood pressure, heart rate, membrane pressure, gas, and temperature monitors (Partridge et al., 2017). One study also used a cardiac ultrasound device about twice a day (Partridge et al., 2017). These instruments are essential to the AP system and reduce physiological stress, as only two cannulas directly connect with the fetus through the umbilical cord.

The surgical procedure involved in human AP fetal procurement could be similar to the experimental procedure previously performed in lambs. In the Partridge et al. (2017) study, pregnant ewes were anesthetized. A small incision was created in the uterus, where the fetus's umbilical vessels were exposed and cannulated with a thin tube placed into the vessel. Once a vascular circuit was established, the fetus was transferred to the fluid incubator. This procedure could be performed very similarly on a human fetus. If a mother has gone into premature labour and childbirth cannot be delayed, a Cesarean section can be performed. A Cesarean section involves the delivery of a baby through a surgical incision in the uterus. The fetus would then be accessed to cannulate and establish blood flow to the vascular circuit. Incubation in the AP equipment would occur until full maturity was reached. If a fetus were undergoing distress or not developing correctly, the fetus could be removed from the AP equipment and the normal NICU procedures could be performed. The initial intent with AP technology is not to extend the viability of ex utero fetuses but to improve the quality of life of infants who would otherwise be in the NICU. The AP's future goals could include extending viability earlier than 22 weeks for fetuses under endogenous placental distress. An example of this viability extension would be the use of an AP with a 20-week fetus that did not adequately receive nutrients from a mother undergoing pregnancy complications.

The far future may involve the use of APs in non-emergent cases where a life has not previously been at risk due to pregnancy complications. This future method would include using IVF techniques to form a fertilized cell bundle. The inner cell mass would then have to be separated from the trophectoderm and attached to a smaller version of the AP equipment. The amount of research on placental mechanisms would have to exponentially increase for APs to become a reality within the next hundred years. As the embryo requires an unknown amount of nutrients, hormones, and gas exchange, these amounts would first have to be determined for every single day of pregnancy. The placenta and embryo rapidly and drastically change throughout the first two trimesters of pregnancy. The AP equipment would also have to replicate these uterine functions. The preterm AP functions differently, as the third trimester of pregnancy still requires many unknown additional molecules. However, most organ development is normally differentiated at this time. In the third trimester, the fetus mostly increases its body fat and undergoes slight organ development. If the AP process starts with a five-day-old embryo,

the complete development of all organs must be achieved, and this process requires a much more intensive understanding of the mechanisms of development than modern science currently possesses. The 'Biobag' used would have to either expand with the growing fetus or be switched out to accommodate the size growth. Each nutrient would have to be administered through the AP. This process would also likely require much more extensive medical equipment.

Ethics

The development of an AP could bring many physiological benefits to preterm babies, but physiological manipulations come with ethical considerations. The four bioethics principles by Thomas Beauchamp and James Childress (2013) are autonomy, beneficence, nonmaleficence, and justice. These principles work as a framework for understanding and guiding many medical professionals' moral and ethical principles. Beauchamp and Childress (2013) describe the four moral principles as:

(1) Respect for autonomy (a norm of respecting and supporting autonomous decisions),
(2) nonmaleficence (a norm of avoiding the causation of harm),
(3) beneficence (a group of norms pertaining to relieving, lessening or preventing harm and providing benefits and balancing benefits against risks and costs), and
(4) justice (a group of norms for fairly distributing benefits, risks, and costs). (p. 13)

Autonomy creates negative and positive obligations for medical professionals. Negative obligations include the obligation not to coerce or constrain an individual, and positive obligations include professionals' obligation to educate patients and ensure informed, self-governing decision-making occurs (van Manen, 2020). In nonmaleficence, harm can be associated with physical, mental, and overall well-being. The professional has a negative obligation not to act in a way that can damage pa-

tients. Nonmaleficence is the basis of the Hippocratic oath that physicians must take. Beneficence carries a positive obligation for professionals, as they must act to prevent harm and to benefit their patients. The final principle is justice, which includes a positive obligation, as the individual must have fair and appropriate treatment or distribution of benefits owed to them. This fair treatment must also distribute any societal or individual burdens. Different aspects of AP ethical dilemmas will be examined with these four ethical principles.

Autonomy

One of the most discussed moral principles pertaining to preterm infants is autonomy. As autonomy refers to an individual having liberty (freedom) and agency (self-initiated deliberate actions), some people believe that an infant does not obtain autonomy (van Manen, 2020). Infants are reliant on parents and, therefore, do not have liberty or agency. This reliance indicates that parents have complete control over their child's life decisions. The other side of the debate mentions that even if an infant does not currently have autonomy, they will when they grow up. This concept can be examined both ways. In Canada, the parent's autonomy is respected, provided that the parent makes reasonable choices and does not use their child for secondary gain (van Manen, 2020). With AP technology, autonomy could easily depend on the fetus's parents. As the fetus is unable to make informed decisions, the parents must decide for it. It would likely be up to the parents to decide if a preterm infant was added to an AP. When the infant grows up, they may feel their autonomy was taken away from them or disagree with their parents' choice. A preterm infant whose parents did not decide to use an AP could also raise the issue that their parents did not respect their future decision-making ability. As the healthcare professional is responsible for the patient's autonomy, not the parents, many ethical dilemmas may occur. Many of these ethical concepts can also be applied to full-term AP scenarios, as people have even more controversial and divided opinions on whether embryos have autonomy.

Nonmaleficence

Nonmaleficence pertains to inflicting the least amount of harm possible and is significantly present in AP technology. As the procedure requires needle insertion, it can cause immediate or permanent damage through complications. Prolonging a suffering fetus's life in an AP could also cause harm. The use of AP technology on humans would require some testing on humans. This testing would occur after rigorous experiments were performed using other methods but would still come with risks to the fetus. Nonmaleficence could also indicate that not using AP technology when it is available could cause undue damage to that developing infant. The use of APs for preterm infants is generally considered nonmaleficence, as it attempts to decrease the physiological stressors or harms faced by those individuals. Many modern AP research projects intend to help emergent cases by eliminating potential harms. When APs are used for non-emergent patients, determining nonmaleficence is more complicated. It is not clear if a full-term AP scenario would directly cause any harm to the fetus. The separation of the inner cell mass may cause undue harm to an embryo that could be left alone through the natural process of pregnancy. If an individual predisposed to harmful pregnancy complications wants to have a child, it may be less damaging to use the AP than to risk endogenous complications. This fact could be true in any pregnancy, as the natural process will always come with risks of harm. The natural process of pregnancy can have risks associated with fetal distress, but faults in the AP procedure can also potentially harm the embryo. A more precise understanding of APs' potential risks may need to be reached before this technology can be determined to be non-maleficent.

Beneficence

In fetal development, determining a viewpoint on life is essential for establishing beneficence. Beneficence can be understood through three different views: vitalism, sanctity of life, and instrumentalism.

The vitalism view indicates that all life is important, no matter the form or consequences (van Manen, 2020). Vitalism supporters would use APs in any scenario due to the importance of life. Even if harm or negative consequences were to occur from AP use, life would be sustained. This viewpoint has an obvious and broadly accepted answer to the issue of whether to use APs.

Sanctity of life viewpoints look at the worth of a life, but also use distinctions between ending and prolonging life (van Manen, 2020). Extinguishing life is not allowed, but prematurely ending someone's suffering by limiting measures that prolong life is allowed (van Manen, 2020). This viewpoint would not be against APs if they prolonged the natural events of life in a positive manner and is based upon the requirement that life must be of value if it is established as good (van Manen, 2020). A good life can be extended, and a life that is void of quality can be ended (van Manen, 2020). This quality of life can be physical, mental, spiritual, and approached through many other modalities.

Instrumental views are where this scenario becomes the most complicated. An infant could be placed in an AP to extend their life as long as the infant's quality of life could be preserved or improved to an acceptable level. The instrumental view looks at a case-by-case basis of AP use. This view is most likely what healthcare professionals would use. If a fetus that were to undergo the AP procedure would suffer excessively or endure a prolonged poor quality of life, AP would likely not be performed. In situations involving genetic abnormalities that cause unviable fetuses to grow, the use of APs would not be beneficial. This issue may change in full-term AP use if the genetic abnormalities could be fixed or altered before implantation.

Justice

The use of APs in a way that promotes justice would mean the technology would have to be available to all individuals. This universality may not be physically possible, as every preterm infant would require

a large amount of equipment and money. The best thing that any healthcare provider can do is create a triage list that is not influenced by money, status, race, or anything other than the fetus's ability to survive. Promoting justice means that anyone on the list will share the burden created by making it onto the list. Survivor's guilt may become a factor in individuals or families that do receive APs. This procedure would also be expensive. It may be that only wealthy families would be able to afford this treatment if it were not covered by health insurance. Currently, IVF is not covered, which indicates that the more expensive AP procedures would also likely not be covered. These costs would then come out of the parents' pockets, and APs would only be available to those who could afford the procedure. For justice to be upheld, each fetus must be provided the same opportunity to use an AP regardless of its parent's income, its parent's opinions, and medical resources available.

Far Future of Artificial Placentas

The majority of this paper analyzes a near-future concept of preterm APs, but an additional far future can also be examined. The idea of an AP that is used throughout an entire pregnancy is currently only a matter of science fiction. The preterm AP would be a massive step towards making the science fiction topic a reality. In recent years, scientific advancements and studies on AP systems have been explored extensively. In 2021, Nature published multiple papers reflecting current advancements that could be utilized in AP technologies. One of these papers involved the development of mice grown in artificial uteruses for nearly half of the mice's gestational period (Aguilera-Castrejon et al., 2021). Another study from 2022 expanded upon this concept by using stem cell-derived embryos in an artificial uterine environment to develop embryo models with beating heart and brain tissue-like structures (Amadei et al., 2022). Although these are huge advancements for the field, so far they are not aimed towards the full-term development of an embryo. Full development outside of a

uterus is still hindered by ethical boards and laws in multiple countries prohibiting human embryo growth past 14 days, but this topic is being widely discussed for extension (Appleby & Bredenoord, 2018). These recent studies have had a huge impact on the field of developmental biology and have accelerated the timeline of APs' journey to becoming a reality.

AP equipment is constantly being improved and modified to potentially allow even earlier pregnancies to become viable. This improvement can be expanded upon until the blastocyst stage. The development of a full-term AP would require a further expansion of the ethical considerations proposed above. Full-term APs would also have an enormous impact on women's roles in society. If the female uterus were no longer essential for fetal development, many more individuals could have biological children. The separation of mother and child would have to be examined. Parents who have a child in the NICU have been found to often feel unhappy, inadequate, and alienated from their child (Obeidat et al., 2009). The psychological impacts of seeing a child develop in a machine and of not having a physical connection to that child could be detrimental to the parent-child relationship. Breastfeeding would also not be initiated in these mothers. Some of the ethical dilemmas that would need to be examined could be studied in families that adopt children. Adoption could be seen as a similar disconnect of the physical connection between the mother and the child to the situation of APs, and breastfeeding is not induced in this case either. The impacts of seeing a child grow in a machine could be compared to the findings of studies done on NICU patients.

Conclusion

AP research has existed for over 50 years, but only recently have significant, field-changing experiments been conducted in this area. The development of preterm lambs in APs has significantly increased the likelihood of these technologies existing in the future. This study could be the basis for how human

AP techniques will be applied in the future of medicine. The development of AP technologies for use in non-emergent cases would be much more complicated and would require an almost unattainable amount of information to perform safely. The ethical considerations of AP use become exponentially more complicated as AP technology advances. It is debated whether autonomy should rely on parental wants or the wants expected of fetuses. Understanding of beneficence relies on what perspective or view of life an individual holds. Nonmaleficence in emergent cases is much easier to accomplish than in non-emergent cases. The consequences and benefits of AP technology must be shared with all individuals. The real-life implementation of AP technology may be more intricate and controversial than in fiction, but advancements may soon rival Huxley's (1932) depiction in the near future.

Acknowledgments

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