ALTERNATIVES TO USING ABORTED FETAL TISSUE FOR RESEARCH

 Tara Sander Lee, PhD  David A. Prentice, PhD

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EDITORS NOTE

This resource from CBHD is part of a larger research project entitled, *Fetal Tissue Research and Christian Bioethics: A Review of the Scientific Developments, Policy Landscape, and Ethical Considerations (2022 Edition)*.

Introduction

Many ethical human tissue alternatives that do not rely on elective abortions are available to researchers. A recent review in *Issues in Law and Medicine* highlights these alternatives showing that in scientific value, they far outweigh using aborted fetal tissue in research.[1] The alternatives discussed in this article include adult stem cells, induced pluripotent stem cells (iPSCs), humanized mice, and tissue donation from medical procedures or post-mortem individuals who die of natural causes. None of these pose the ethical concerns presented by reliance on tissue harvested from elective abortions. These alternatives exist now and are currently being used worldwide for research and clinical studies. For example, researchers have successfully used these ethical alternatives to study neurodevelopmental disorders,[2] immune response to pathogens,[3] and stroke.[4]

Numerous animal models serve as alternatives to using fetal tissue for research purposes. For example, both vertebrate (e.g., non-human primates, rodents, frogs, fish, etc.) and invertebrate (e.g., yeast, bacteria, worms, flies, etc.) animals are used widely in academic medicine to study disease. For the purposes of this article we will limit our examination to human tissue specimens that can be obtained without ethical controversy and have been used to good effect in experiments simila
fetal tissue.

Adult Stem Cells

Stem cells are cells with differentiation potential: they can give rise to many different types of specialized cells in the body. Some stem cells have more potential than others and can develop into a greater number of specialized cells. For example, epiblast cells from the early human embryo are pluripotent with great potential to give rise to all cell types present in the fully developed human body. Stem cells in the developing fetus are more tissue-specific than embryo epiblast cells, with a varying degree of differentiation depending on the tissue type and fetal age.

Adult stem cells are found in late-development fetal tissues, perinatal tissues (e.g., umbilical cord blood, amniotic fluid, or placenta) and postnatal tissues (e.g., peripheral blood, bone marrow, skin, fat, heart, liver, etc.). Present in virtually every tissue of the postnatal human body, adult stem cells are important for tissue maintenance, regeneration, and repair. They are also unique. Unlike early embryonic or fetal stem cells, adult stem cells can be either unipotent (producing only one type of differentiated cell) or multipotent (producing many different types of cells in a given tissue). This unique ability to self-renew (replicate themselves), while simultaneously dividing to produce other mature, tissue-specific cells, is the reason adult stem cells have become the standard of care in clinical medicine to treat various blood disorders and cancers. Furthermore, they can be obtained ethically from living, consenting adults, without deliberate harm or risk to the individual.

Adult stem cells from bone marrow and cord blood have saved the lives of over 1.5 million people worldwide.[5] Because of these features, adult stem cells are an ideal candidate for several therapeutic and research applications. For example, bone marrow contains multipotent hematopoietic stem cells that give rise to the different types of blood cells (i.e., red blood cells, white blood cells, platelets, etc.) in the human body. Bone marrow transplant procedures rely on "healthy" adult stem cells to replace "diseased" blood cells and treat various disorders and cancers, including treating affected individuals *in utero*.[6] In another example, cord blood from labor and delivery is a highly enriched source of adult stem cells and an important treatment option for a number of diseases, including blood disorders, diabetes, and traumatic brain injury.[7]

Mesenchymal stem cells (multipotent stromal cells, most often isolated from bone marrow, umbilical cord, and adipose [fat] tissue) are another type of adult stem cell that provides an important alternative to aborted fetal tissue in research. They are fibroblast-like, with remarkable plasticity, and have been shown to differentiate into a variety of different cell types of mesodermal (bone, cartilage, muscle), neuro-ectodermal (neurons, astrocytes, and oligodendrocytes), or endodermal (hepatocytes) origin. For this reason, mesenchymal stem cells have shown incredible potential for research and clinical applications in adult stem cell-based therapy of immune-mediated diseases, including graft-versus-host disease (GVHD), inflammatory bowel disease, liver disorders, cardiac diseases, and more.[8]

Stem cells are not inherently controversial in and of themselves; it is how the cells are obtained that determines whether their use is ethical or not. Therefore, adult stem cells (or cells that are more differentiated than embryonic stem cells, but less differentiated than adult somatic cells) obtained from an aborted fetus or from perinatal tissue obtained after an abortion are not a suitable ethical alternative to fetal tissue.

Human Induced Pluripotent Stem Cells (hiPS

Human induced pluripotent stem cells (hiPSCs) are adult somatic cells (i.e., any cell other than reproductive cells, such as human skin cells) that have been genetically reprogrammed into pluripotent stem cells with basic biologic properties similar to human embryonic stem cells (hESCs).[9] Human iPSCs are morally superior to hESCs and aborted fetal-derived tissues and cell lines because their generation does not rely on the deliberate destruction of human embryos or fetuses. Furthermore, they can be generated from nearly any adult somatic cell type and differentiate into various types of cells. There is the real potential for use of hiPSCs in cell-based therapies, disease modeling, and regenerative medicine for a number of diseases, including macular degeneration, ischemic heart disease, diabetes, and spinal cord injury.[10] Human iPSC disease models can also be developed by reprogramming somatic cells from a patient with disease (e.g., skin cells from a Parkinson's patient), a tool researchers can use for understanding basic mechanisms of disease, performing experiments that aim to correct the disease via gene therapy, as well as high-throughput screening of compounds for drug discovery.[11] Induced PSC are a good alternative to using aborted fetal tissue for research and possibly even clinical applications, considering that previous attempts using aborted fetal tissue transplantation have failed to alleviate Parkinson's symptoms. It is important to note that hiPSCs are ethical so long as they are not made using cells isolated from aborted embryos or fetuses.

Organoids

Organoids are another useful alternative that can perform the functions of embryonic- and fetal-derived tissues. Organoids are three-dimensional cellular clusters that have been demonstrated to model normal developmental progression as well as many observed functions for a growing number of human organs and tissues, including brain, liver, pancreas, intestine, stomach, lung, kidney, and eye.[12] These unique cellular constructs can be generated from hiPSCs or adult stem cells derived from ethically donated cells and tissues. Organoid constructs have proven successful in modeling complex mechanisms, disease, and early development,[13] including hepatic (liver) development and nephrogenesis, neurodevelopmental (brain) disorders, retinal (eye) development, and cancer.[14] In one example, aggregation of hepatocytes (liver cells) into three-dimensional organoids can potentially serve as a model for liver function, as bioartificial livers for toxicity testing and possibly transplantation for liver regeneration. Hepatocytes can be produced in culture from umbilical cord blood stem cells.[15] Another example is generation of kidney organoids that contain kidney-specific cell types and structures, similar to that observed in adult kidneys.[16] Other functional human organoid examples include islet-like organoids that restore glucose homeostasis in diabetic mice,[17] hormone-producing thyroid organoids,[18] and tear duct organoids that produce tears.[19]

Cerebral (brain) organoids have been used to study Zika viral infection, test potential treatments and preventative measures, and show cellular complexity of the human cortex, including modeling of normal development.[20] More recently, organoids of the lung, liver, kidneys, and gut have been generated to study how the SARS-CoV-2 virus that causes COVID-19 infects host cells, replicates, and contributes to disease.[21]

Compared to aborted fetal organs (i.e., livers, brains, kidneys, lungs, eyes) used in research, organoids offer a direct alternative for basic observational science experiments, human development studies, testing of pharmaceuticals, and potential clinical applications in regenerative medicine. Furthermore, organoids are ethical so long as they are *not* made using embryonic stem cells,
deliberate destruction of early human embryos.

Human Immune System (HIS) Mice

Human Immune System (HIS) mice, or "humanized" mice, are generated by implanting human tissues and/or cells into an immune-compromised mouse to study infection, disease, and immune response, and to test therapeutics. Humanized mice are used to model HIV infection and test anti-HIV-1 drugs. The "BLT mouse," perhaps the most highlighted model for HIV research, is generated using fetal bone marrow/liver/thymus tissues from second trimester aborted fetuses. However, ethical alternative models exist using postnatal tissues and stem cells, with no need for fresh fetal tissue from aborted fetuses.[22]

There are several different types of HIS mouse models applicable for various studies and available commercially.[23] For example, the "hu-PBMC" or "hu-PBL" mouse uses peripheral blood mononuclear cells (PBMCs) collected from living adults. Another model is called the human hematopoetic stem cell or "hu-HSC" mouse, generated using $CD34^+$ stem cells obtained from adult bone marrow, umbilical cord blood, or peripheral blood. Genetically engineered NSG-SGM3 mice engrafted with $CD34^+$ stem cells from cord blood are also available.[24] More recently, the "NeoThy" humanized mice can be generated using surplus human thymus tissue from newborn babies (neonatal thymus) obtained during surgical procedures to repair congenital heart defects, combined with HSCs from cord blood.[25] Neonatal thymus tissue is abundant and 50 times more efficient than aborted fetal tissue for generating the same number of mouse models—an important benefit for reducing experimental variability.[26]

In general, there are limitations to all HIS mouse models, whether made from fetal tissue or not. However, humanized mice generated with aborted fetal tissue (i.e., BLT mice) tend to be more technically difficult, costly, and time consuming to make compared to other models.[27] There are several technical advantages to using alternative models (e.g., hu-HSC mice). For example, they are easier to prepare at lower cost and more animals can be generated per cohort. Some studies have also observed negligible graft-versus-host disease, longer life span, and greater longevity with chronic HIV infection.[28] HSCs from umbilical cord blood has also been reported as the better scientific and ethical source for optimal human cell engraftment compared to aborted fetal liver tissue.[29] Investigators recognize that HSCs from fetal liver can easily be replaced with HSCs from umbilical cord blood when generating HIS mice.

Post-Mortem Tissue Donation

Postmortem tissues from prenatal or postnatal deaths that occur naturally and do not involve deliberate destruction of human life are an ethical alternative to fetal tissue obtained from abortion. Furthermore, prenatal and neonatal tissues from natural death (i.e., ectopic pregnancy, miscarriage or spontaneous abortion, or stillbirth) are more widely accepted and approved for use in research, with no apparent state statutory restrictions, unlike fetal tissue obtained from elective abortions.[30] Historically, human tissues from miscarriages and full-term stillborn infants have been collected, processed, and used for various research studies dating back to the 19^{th} century.[31] These early studies examined the feasibility of using miscarriage tissue to study cell viability, disease mechanisms, and even transplantation. And while not always successful, they proved that fetal tissues could be obtained from miscarriages and cell lines could be established for experimentation. Some studies with miscarriage tissue even showed comparable results to fetal tissues from surgical abortions.[32] Later studies examining a larger number of miscarriages and ectopic pregnancies found that 63% of identifiable embryos/fetuses
viable cells and tissues from various organs (i.e., liver, thymus, splee

spinal cord, kidneys, lungs, and skin).[33] Based on this percentage, tens of thousands of miscarriages with quality tissue could be available per year in the United States.

Miscarriage tissue has been examined for suitability for transplantation studies. A 1995 *JAMA* article reported the examination of over 1,000 spontaneously aborted embryos (miscarriages) and ectopic pregnancies and found that a limited amount of miscarriage tissue would be suitable for clinical transplants.[34] Other investigators refuted these findings and reported that second-trimester miscarriages were in fact suitable for transplantation when collected and preserved properly,[35] resulting in the establishment of a small cell bank to provide hematopoietic stem cells from second-trimester miscarriages for these studies.[36] Nevertheless, these studies provide further evidence that fetal tissue from miscarriage tissue is accessible and obtainable.

Additional reports using miscarriage tissue have demonstrated that researchers can transplant fetal bone marrow HSCs into sheep,[37] cerebrum (also known as telecephalon) can be isolated from fetal brain to detect astroglia cells,[38] and human midbrain-derived neural progenitors (hmNPCs) can be generated from fetal central nervous system tissue.[39] Finally, two different groups have isolated human neural stem cells (hNSCs) from miscarriage tissue; one of these studies even describes using these cells as a test of safety for cell therapy in a phase I trial which could then lead to later-phase clinical trials for the treatment of patients with ALS.[40]

There is some concern over genetic abnormalities as the cause of miscarriage, leading certain researchers to avoid miscarriage tissue altogether. However, the majority of genetic aneuploidies (abnormal chromosomal number) occur in the first trimester. Furthermore, the CDC reported in 2014 that only 10% of fetal deaths in the second trimester at greater than 20 weeks' gestation are attributed to congenital malformations and chromosomal abnormalities.[41] Most fetal deaths were found to be a result of physical or environmental factors rather than genetic issues, including such factors as placenta or cord complications, maternal complications, or conditions related to pregnancy.[42] In fact, the largest NIH-funded fetal tissue repository in the United States, The Birth Defect Laboratory at the University of Washington, considers tissue from both elective abortions and natural miscarriage as acceptable tissues for their bank.[43]

Finally, postnatal cadavers from deaths due to natural and unexpected causes are suitable for several research applications. In a retrospective review, Hodgetts et al. found that stem cells could be isolated after death from neonates to adults 95 years of age from various organs including eye, brain, muscle, arteries, and pancreatic islet.[44] There are other examples of postnatal cadaveric specimens collected and analyzed together with fetal tissue from elective abortions, particularly in large developmental genomic and proteomic studies.[45] For example, in 2018, Li et al. created a genomic dataset from tissues and cells collected from 60 de-identified postmortem brains ranging from five post-conception weeks (PCW) to 64 postnatal years (PY) in which 50% were postnatal cadaveric tissue collected from natural deaths. They concluded that their genomic dataset allowed them to gain "insights into human development and disease" and "insights into neurodevelopment and the genomic basis of neuropsychiatric risks."[46] The ethically alternative cadaveric tissue of infants, children, and adults that died of natural causes was considered equivalent and matched to the unethically obtained aborted tissues, thus demonstrating that post-mortem tissues from individuals who die of natural causes are a suitable and good alternative to aborted fetal tissue.

Tissue Donation from Medical Procedures

Researchers have access to ethical human tissues obtained from living, consenting individuals after medical procedures, often available through tissue banks at their own academic institution. Such human tissue specimens from medical procedures can be stored in a secure storage facility that collects, processes, and distributes discarded human tissue samples donated by patients from labor and delivery procedures (such as placenta, cord blood, and umbilical cord), as well as routine surgery and biopsy procedures that require the resection, sampling, or removal of tissues as a part of the surgical method (i.e., cardiac, neonatal thymus, abdominal artery, bladder, adipose, tonsil, liver, and tumor). Unused discards from explanted organs from organ transplant procedures are also an important source of human tissue for research.

Tissue banks are known to manage patient consent and perform collection of blood products and otherwise discarded tissue from surgeries, including bone marrow, tumor, and control tissue. Tissues may be available to researchers at no charge or, at most, reduced cost to cover storage fees. Alternatively, researchers may choose to work closely with clinical departments (i.e., surgery, pathology) at their own institution in order to establish project-specific patient consent, tissue collection, and processing procedures with proper institutional review board approval. This option is important if unique human tissue specimens are desired and not available through a repository or tissue bank.

National tissue repositories are another option to researchers. The National Marrow Donor Program (NMDP)/Be the Match is the largest repository for cord blood available to clinicians and scientists worldwide for transplantation, cellular therapy, and research.[47] The NMDP-Be the Match repository also processes and stores tissue, cells, and DNA samples from donors and recipients who are in the process of providing or receiving stem cells for transplant, of which some are available to researchers for experimentation.[48] In another example, the NIH-funded NeuroBioBank (NBB) is a national resource for investigators utilizing human post-mortem brain tissue and related biospecimens for their research to understand conditions of the nervous system.[49] The NBB also collects and stores fetal brain tissue, but a researcher can avoid these tissues and specifically request ethically obtained alternatives, such as brain tissue collected post-mortem from adults with Parkinson's Disease or major depressive disorder, as well as age-matched controls.

Commercially available cell repositories that clearly label the source of the donated cells or tissue are another option for researchers, although extra steps may need to be taken by the researcher to ensure the human-derived material indeed comes from an ethical source. Examples include American Type Culture Collection (ATCC)[50] and Coriell Institute for Medical Research (Coriell Institute) with more than 11,000 unique samples donated by different individuals for the production of cell lines and genomic DNA. [51] As mentioned previously, these vendors also provide fetal-derived cell lines from elective abortion (i.e., HEK293), but with careful analysis of the product sheet description, cell lines derived from aborted fetal tissue can be avoided. Special attention must be made to donor age at time of sampling or collection. Any age with the term "fetus" or Fetal Week (FW), without mention of a natural death (i.e., miscarriage, stillborn, neonatal death), is questionable. Databases like Cellosaurus (a knowledge resource on cell lines) and technical support staff should also be queried for additional product information when needed.[52]

Conclusion

Several ethical alternatives to abortion-derived fetal tissue are availa
and even treating, some of the most complex diseases and disorders.

stem cells, cord blood, hiPSCs, organoids, and humanized mice generated with ethical sources. The majority of scientists are focusing on these ethical tissue sources and models that work just as well as, if not better than, aborted fetal tissue. And in cases where alternatives to fetal tissue cannot be used, fetal tissue obtained post-mortem from natural deaths is a useful and ethical solution.

After over 100 years of research, no therapies have been discovered or developed that *require* aborted fetal tissue.[53] Ample scientific evidence points to numerous valuable ethical alternatives that are available, successful, and even more advanced. The utilization of these current ethical alternatives, active avoidance of aborted fetal tissue, and development of new and even better alternatives will safeguard against controversies that surround the exploitation of aborted fetuses for experimentation and clinical application.

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