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Reflexive Research Ethics in Fetal Tissue Xenotransplantation Research

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Abstract

For biomedical research in which the only involvement of the human subject is the provision of tissue or organ samples, a blanket consent, i.e. consent to use the tissue for anything researchers wish to do, is considered by many to be adequate for legal and IRB requirements. Alternatively, a detailed informed consent provides patients or study participants with more thorough information about the research topic. We document here the beliefs and opinions of the research staff on informed consent and the discussion-based reflexive research ethics process that we employed in our fetal tissue xenotransplantion research on the impact of environmental exposures on fetal development. Reflexive research ethics entails the continued adjustment of research practice according to relational and reflexive understandings of what might be beneficent or harmful. Such reflexivity is not solely an individual endeavor, but rather a collective relationship between all actors in the research process.

Keywords

Informed Consent; Bioethics; Research Ethics; Reflexive Research Ethics; Fetal Tissue Transplantation

INTRODUCTION

Fetal tissue transplantation offers unique research opportunities for exploring fetal development and epigenetic changes that stem from common environmental exposures and other stressors. However, fetal tissue transplantation is controversial with ethical, moral and socio-political considerations that are different from other human- and animal-based research. Fetal tissue research calls attention to concerns over sentient life, abortion, religious beliefs, ownership of the tissue, and who has the right to decide to donate tissue. There are, of course, feelings of loss of the fetus. Blanket informed consent for tissue donation is preferred by many, however, it does not require that information specific to the use of fetal tissue and transplantation be provided to the parents who donate fetal tissue (Beskow et al. 2010, NCI 2011) How much should parents who donate fetal tissue be told about the proposed nature of research for which the tissue will be used? How should the researchers discuss, decide, and address complex ethical issues in fetal tissue research? This research reports on the “reflexive research ethics” process (Cordner et al. 2012) employed by a multidisciplinary research team that explores environmental stressors and their impact on fetal development. We developed the concept of reflexive research ethics, which involves the self-conscious, interactive, and iterative reflection upon researchers’ relationships with research participants, relevant communities, and principles of professional and scientific conduct. Reflexive research ethics entails the continued adjustment of research practice

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according to relational and reflexive understandings of what might be beneficent or harmful. Such reflexivity is not solely an individual endeavor, but rather a collective relationship between all actors in the research process.

The Work of the Research Team

Environmental health researchers and health professionals from Brown University, Rhode Island Hospital, and Women and Infants Hospital collaborated in 2010 to form the Children's Environmental Health Center, jointly funded by the Environmental Protection Agency and the National Institute of Environmental Health Sciences. The Center's research is based on the "Barker hypothesis," which examines the fetal basis of childhood and adult diseases (Barker 1992). The Barker hypothesis looks at how a mother's body composition, diet, and fetal exposure to different pollutants in the environment can affect genes and ultimately the future health of the fetus. Fetal programming is presumed to be an adaptive response to environmental cues, acting predominantly through epigenetic mechanisms that regulate the expression of genes via multiple mechanisms, such as DNA methylation, histone modification, and microRNA modulation. Epigenetic modifications are responsible for childhood and later life patterns of metabolism, cell proliferation and growth, and immune and injury responses that can ultimately act as predisposing factors in disease.

The Center is built around four components: an Administrative Core, a Tissue Procurement Core, a Xenotranplant Core, and a Community Outreach and Translation Core. The larger research team comprises a multi-institutional and interdisciplinary group including toxicologists, pediatricians, obstetrician-gynecologists, pathologists, transplantation laboratory scientists, and sociologists. The Community Outreach and Translation Core comprises a sociologist and a postdoctoral environmental health scientist, who were assisted by an undergraduate student. The community outreach activities include the translation of laboratory observations and broader children's environmental health issues to clinically relevant and community appropriate responses, with the goal of improving public health. The sociologist (PB) who directs the Core has extensive experience in research ethics issues that involve alternative approaches to informed consent. He and the postdoc (BP) have extensive experience in community-based participatory research, which pays much attention to ethical concerns such as patient right-to-know.

The Tissue Procurement Core facilitates tissue collection and processing of biological samples for the study. Human fetal tissues collected for study from spontaneous abortions are of 12-22 weeks gestation. Permission is sought for the collection and use of these fetal tissues from parents who donate fetal tissues. Samples collected include prostate, lung, liver, breast, and ovary tissue specimens from spontaneous abortions that occur at Women and Infants Hospital. The aborted fetus is processed at the hospital as part of the usual clinical processing for pathological evaluation within 4-18 hours of delivery for study purposes. The tissues procured for the purposes of this study are considered de-identified residual tissue.

Next, the Xenotransplant Core prepares selected tissues for immediate xenotransplantation into immunodeficient rodent hosts, after which the transplanted tissues are exposed to common environmental pollutants and stressors (e.g. arsenic, lead, phthalates) to assess the human fetal tissue responses. This method of xenotransplantation allows for more realistic assessment of human health effects, since it involves experimentation on human cells in animal hosts. This differs from the traditional animal model where high doses are given to animals and the results extrapolated to human risk estimates. The projects undertaken by this team investigates human fetal liver and the metabolic syndrome, human fetal prostate and endocrine disruption, human fetal testis and phthalate exposure, human fetal lung, arsenic exposure and tissue remodeling, endocrine disruption effects on ovaries, and endocrine disruption effects on mammary gland. These studies look into the underlying mechanisms of

environmentally-induced fetal disease. Importantly, this biomedical research offers no direct therapeutic benefits to participants, and offers benefits only to science in general.

Grappling with Ethics

As the team was writing the proposal for the Center, a yearlong process, the question emerged on how much to tell the parents about the research when asking for permission to use tissue from their fetuses. Two approaches to informed consent were initially considered; one that simply obtained blanket permission from parents for any and all uses of the tissue, and the other approach offered detailed information on the nature of research to the parents while seeking consent, what we term "detailed consent." It was clear that the university and hospital IRBs would have approved the project with blanket consent. Detailed informed consent was a new area of discussion for some of the research team members, though physicians had experience in medical ethics. It became clear during research group meetings on ethics that the question of informed consent was not just a logistical issue for the team, but also an opportunity for ongoing research and education of the group, the hospital staff and the participants who donated tissue. The research group discussions on research ethics in this case influenced the team's decision to offer detailed informed consent to parents who donated fetal tissues. The Community Outreach and Translation Core, which serves to engage the scientific and general communities in this research, adopted this issue as a research project and proceeded to document the discussions on research ethics among research participants and further interviewed research team members and the parents who donated fetal tissue on their views on detailed informed consent. Interviewing the project staff brought to light the various ethical concerns that the staff reflected on within the process of seeking detailed informed consent. It also provided the Outreach Core with a way to evaluate the effectiveness of the team's approach.

This article reports on the beliefs and opinions of the research team on how to engage in informed consent; a later article will report on the experiences of the participants who donated fetal tissue. We especially emphasis the "reflexive research ethics" process used in the team's discussions on informed consent. Reflexivity in this case encourages transparency and reflection on ethics at all stages, starting early on in the research design process, and continuing as the project unfolds and the team gains experience in discussing detailed consent with potential tissue donors and with other hospital colleagues not involved in the Children's Center. Reflexive research ethics aims to promote active dialogue on purposes, processes and outcomes between the work teams and participants as an ongoing initiative that facilitates personal, professional and system changes.

Issues in Fetal Tissue Research

Use of human fetal tissues for research has been legal since the 1930s (American Society for Cell Biology, 2001). Polio vaccine was developed using human fetal kidney cells that led to the 1954 Nobel Prize in Medicine. Other vaccines, such as those for rubella and varicella, which have greatly controlled major sources of child morbidity and mental retardation in the US, were also made from fetal tissue cultures (Coutts 1993). Fetal tissue research has also offered valuable insights into birth defects and other developmental diseases. Fetal tissue and embryos for research can be obtained from a variety of sources including hospitals, non-profit tissue banks, and in some cases abortion clinics and fertility clinics.

This project uses fetal tissue transplantation to assess the environmental impacts on fetal development and epigenetic changes. Fetal cell research holds unique promise for biomedical and environmental health research to explore fetal development and epigenetic changes that stem from common environmental exposures and other stressors. Fetal cells are

less susceptible to rejection and they proliferate and adapt much more easily than adult cells, which is why fetal tissue is so valuable for such research.

But these benefits come up against key obstacles. Fetal tissue transplantation into animal models such as rodents is a highly charged and controversial topic, with ethical, moral and socio-political implications that are more powerful than other human- and animal-based research. The use of fetal tissue in research has been highly politicized in the US, inflamed by the highly polarized abortion debate in this country in the wake of *Roe vs. Wade* and the controversial debate on the morality of stem cell research. Some who oppose the use of miscarried fetal tissue for research and transplantation do so because it is inextricably linked to the controversy over abortion (Verklan 1993).

Since 1975, federal law requires permission or accordance with applicable state laws regarding fetal tissue research (45 C.F.R. 46. Sec 210). Almost half of the states in the US have fetal research statutes; 12 either prohibit or seriously restrict general scientific research *in utero*, and 18 prohibit it *ex utero* (NCSL 2008; Andrews 1994, 1993). In 1988 President Reagan issued a moratorium on federal funding for fetal tissue transplantation research. This ban, however, did not apply to the use of fetal tissue for other research purposes. It was in effect for five years until the Clinton administration lifted the ban in 1993 under the National Institutes of Health Revitalization Act (Public Law 103-43), which amended the Public Health Service Act and allowed support for research on transplantation of human fetal tissue for therapeutic purposes. This Act also allowed the use of tissue from both spontaneous and induced abortions, as well as stillbirth (42 U.S.C. 289 et seq). Since 1999, forces both inside and outside Congress opposed to any scientific use of fetal tissue have tried to make an issue of the supply of fetal tissue to researchers, denouncing those involved as engaged in “the sale of baby body parts.” During the 2000 campaign, candidate George W. Bush was opposed to any use of fetal tissue or embryonic stem cells for research. Under the current law, it is “unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable (profitable) consideration if the transfer affects interstate commerce” (Hurd 1992; American Society for Cell Biology 2001; Boonstra 2001).

Human research involving stem cells derived from human embryos or human fetal tissue research must be in accordance with the Department of Health and Human Services (HHS) regulations for the Protection of Human Subjects (45 CFR,Part 46), FDA regulations (21 CFR 50 and 56) for fetal tissue based clinical research involving drugs, and the informed consent regulations (OHRP 2001). The use of human fetal tissue and transplantation is governed by the Uniform Anatomical Gift Act of 2006 which allows donation, provided parental consensus is obtained (Verklan 1993). This stems from the 1993 statute’s requirement that the woman donating her human fetal tissue must sign a statement declaring that the tissue is being donated for scientific research. The donation is to be made without disclosing the identity of individuals who may be the recipients of the transplantations. Human fetal tissue may be used only if the head of the agency or other entity conducting the research certifies to the Secretary of Health and Human Services that those requirements will be available for audit (NIH 1993, 45CFR 46.116).

Biomedical research commonly relies on highly specialized biorepositories that allow the secondary use of pathology archives derived from surgical resection specimens or from autopsy (Riegman and Veen 2011). Most studies using fetal tissue gather residual tissues that are routinely collected from these archives. More than 300 million tissue samples are in storage in the US in both public and private repositories with 20 million added each year Many of these were collected during surgical and clinical procedures and has not obtained any consent for research (Eismen and Haga, 1999, Maschke 2008). In the case of using stored data or human tissues, the tissue collectors and repository storage and data

management center's are subject to IRB review, informed consent, certificate of confidentiality and assurance of compliance. Informed consent for repositories include "description on (i) the operation of the cell repository; (ii) the specific types of research to be conducted; (iii) conditions under which data and specimens will be released to recipient-investigators; and (iv) procedures for protecting the privacy of subjects and maintaining the confidentiality of data" (OPRR 1997). In 2004, the US Office of Human Research Protections (OHRP) issued a guidance that coded private information or human biological specimen that are unidentifiable private information not obtained through intervention or interaction with living individuals is not considered human subjects research, in which case IRB review of the research is not required (OHRP 2008, 45 CFR 46.101). This applies also to *in vitro* research cell lines and research in animals using already derived and established human cell lines. They are not considered human subject research and are not governed by the HHS or FDA human subject protection regulations appearing at 45 CFR Part 46 and 21 CFR Parts 50 and 56 (OHRP 2002).

Blanket consent is at the moment considered sufficient consent modality for residual tissue use and the fetal tissues from biobanks if proper governance is assured. An opt-out procedure, which allows the use of residual tissue unless the patient has objected to such use, is formalized in many European countries with the reasonable expectation that the results will come back as treatment available to all in the health-care system which applies more to counties where patients have equal access to healthcare (Riegman and Veen 2011). In the US anonymous residual tissue is not human subject research and hence consent is not required (OHRP 2008, Washington 2011). In recent years such research use of stored residual human cells and tissue has sparked attention, even if it is only slightly different from biobanking for which tissue is specifically collected. The well-known case of Henrietta Lacks, described in Rebecca Skloot's widely-read book, illustrates the abuses of using stored samples for research about which the donor or her surviving family is unaware (Skloot 2010). The use or misuse of these samples has been regarded as the most fundamental concern in the procurement of residual samples, especially with regard to genetic research. With advances in molecular biology and the ability to identify the role genes play in disease formation, there is an accelerated drive towards creating new diagnostic tests, targeted treatments for specific diseases, and possibly even customized personalized medicine (NCI 2011, Maschke 2008). The "Genetic Information Nondiscrimination Act" of 2008 proposes that genetic information is different from other types of personal information and requires protection as the release of genetic test information may adversely affect patients and their relatives. Recommendations to prevent misuse propose that secondary researchers (i.e., those not involved in the collection of tissue) use only coded or anonymized samples, which do not require informed consent for the secondary use (OHRP 2008, Annas, Glantz and Roche 1995; Clayton et al., 1995). However, the controversy in the use of these residual samples include not only informed consent, which is typically thought to have minimal risks, but also privacy, confidentiality, future use, ongoing medical record access, disclosure of research results, intellectual property and biobank governance and the ability to discontinue participation (Maschke 2008, Beskow et al. 2010).

Issues in Informed Consent

Informed consent is central to the issue of the ethics of fetal tissue and xenotransplantation research (NIH guide, 1993, 45CFR 46.116). Since the Belmont Report, informed consent has been described as a form of respecting individual autonomy (Silverman 1989; Davis 2004; O'Neill 2004). Some studies stress that unlimited autonomy should not be imposed necessarily, on the basis that people have limited capacity for completely autonomous behavior and that autonomy can be represented by previous or later preferences (O'Neill

1984; Davis 2004). It is difficult to fully satisfy the principles of beneficence and autonomy in informed consent in a just and healthy manner (Silverman 1989), but a well thought-out process tailored to the specific research context is possible.

An informed consent process that includes more information than the legal minimum may be the right thing to do, regardless of specific regulations. As Lidz et al. (1984) argued in their classic work on informed consent, even if patients do not grasp the details of what they are told, they still have a fundamental right to as much information as the researchers can provide. In following such an approach, scholars increasingly view informed consent as a process rather than simply a form or a single event (Gray 1978; Kuczewski 2002; Matsui 2005). The process should be long-term, educational, and based on mutual trust; ethical concerns should trump scientific needs or agenda (Matsui 2005; Prentice 2007). Challenges in implementing informed consent include adequately explaining critical aspects of the research such as risks, purpose and procedures (Prentice 2007; Pfeffer et al. 1997; Mechanic 1984; Gillett 1989). In particular, research concepts such as clinical trials and randomization, as well as technical and scientific language, are difficult to communicate to patients (Pfeffer et al. 1997; Prentice 2007; Russel et al. 2005). Informed consent material has been difficult for participants to understand based on background factors such as lower socioeconomic status, literacy and language ability (Kuczewski 2002).

Researchers often view ethics as “a rather static set of standards for conduct based on a system of moral values” (Smith-Doerr 2006), established as professional codes of conduct and mandated through Institutional Review Board (IRB) protocols that determine acceptable research practices and their protection of human subjects. Such a structure offers a clear and predetermined set of guidelines for research, but it does not take into account the ongoing reflexivity required of researchers involved in new ethical issues. We propose that reflexive research ethics offer a valuable advance to routine ethics.

Reflexive Research Ethics in Informed Consent

Our concept of reflexive research ethics (Cordner et al. 2012) proposes that researchers must move beyond seeing ethics as static, pre-conceived standards or guidelines, to seeing research as a process that is embedded in social relationships and full of social consequences. Reflexive practice is an exploration of tacit knowledge that becomes clarified with time, experience, and knowledge which has the potential to shape future action with better understanding of the subject matter, relationship with individuals and the situations involved (Schon 1987). Such an activity is transparent and pays close attention to experiential learning of activities carried out as part of one’s profession and questions the ethical and social consequences to research applications. This requires researchers to identify and establish interactive discussions with the full range of parties relevant to their work, including research group members, research participants, local communities, academic disciplines, and those potentially impacted by the research. They must ensure that research participants have not only the right to information but also the capacity to enhance their participation in research and decision-making. They must identify norms and principles that govern their work, evaluate ethical tensions which may arise from the research, and respond to emergent ethical tensions, such as those arising from the study of public engagement with new or emerging technologies in science such as next generation DNA sequencing as well as advances in communications and social media such as chat rooms and tweeting, that influence research participation, data transmission and access. Xenotransplantation research is precisely such an emerging technology. Reflexivity also includes self-conscious and interactive reflection on all the above points, and the continued altering of research practice according to new understandings.

This article explores the social process within the fetal tissue procurement and xenotransplantation research team in building consensus and employing detailed informed consent. The research also explores the beliefs and opinions of the research team members, the evolution of their thinking on research ethics, their tensions, challenges and potential future implications of employing a transparent research methodology. Ultimately, we inquire if reflexivity and ethical considerations motivate the adoption of a transparent research methodology and detailed informed consent.

METHODS

The research team's discussions about ethics started early on, at the proposal writing stage. We built reflexive practice into the research process in order to encourage transparency and develop capacities of reflection on ethics by promoting active dialogue on purposes, processes and outcomes amongst the research team members as an ongoing initiative that facilitates better work ethics. Reflexivity on informed consent has become an ongoing topic of discussion at our regular team meetings as well as at our annual retreats, site visits with the program officers, and other public talks.

Our data include documentation of discussion on research ethics at the research team meetings which were followed by interviews with each of the research members at the Center. The notes on research ethics discussions were taken during the Children's Environmental Health Center team meetings at multiple points in time: the proposal writing, the period between when the grant was awarded and the project procedures were being devised, at many ensuing team meetings, at the annual retreat to which the university and community were invited, and at a later conference that was held as part of an EPA site visit. These meetings were spread over two years, a year before the project got funded and a year after that. Other notes come from meetings with clinical staff at the hospital, when the team was informing hospital clinicians of the project and seeking referrals.

Further, ten members of the research team were interviewed regarding their thoughts on many aspects of the project including the ethical issues involved, the group discussions that originally led to detailed consent, and their expectations for how hospital staff and parents who donate fetal tissue would react to the research. The interviews were conducted in the summer of 2010, a year after the Center got funded. We interviewed all the key research personnel in the Center including project staff from the Administrative core (n=1), Tissue procurement core (n=3) and xenotransplant core or lab scientists (n=6). The Community Outreach and Translation Core staff were not interviewed since they were carrying out this research on the informed consent process. General consensus on detailed informed consent was reached before submitting the proposal for funding and before seeking IRB approval. However, as we found out later from our in-person interviews with research staff, not all were wholeheartedly supportive of that consensus, even though they went along with the decision. The interview process gave team members the chance to revisit their original perspectives, in which they were better able to see that agreement did not necessarily mean deep support of the approach. Still, the consensus agreement was always mentioned in public presentations, and staff were comfortable with that presentation of self.

In addition, we interviewed the recruiter and the parents who agreed to participate in the research and donated their fetal tissues. These interviews were done usually a week or two after their miscarriage. We will report in a later paper on these interviews, though we refer to their findings because the research team learned important data from our analysis and discussion of those interviews. The parents who donated the fetal tissues were enrolled in the study after the research team decided on offering detailed informed consent to the parents who join the study.

The observations on the research ethics discussions were made by the social scientist research on the team. Interviews were conducted by the three authors: the social scientist researcher on the team, a staff person on the Outreach Core who was not on the project team, and a student working on her senior thesis. The interviews were semi structured and were one hour long on average. Oral consent to participate were obtained for all interviews conducted in this study with research team members, recruiter and parents who donated fetal tissues. The interview questionnaires and all study procedures for the research team member interviews and parent informed consent interviews and a follow up interviews with the parents who donated the tissues were reviewed and approved by the Brown University and Women and Infants Hospital Institutional Review Boards.

Data Analysis

All interviews were recorded, transcribed, and coded in NVivo, a software program for analyzing qualitative data. Codes were developed inductively from the empirical data as well as common themes and topics that emerged from the research team discussions and interviews. Preliminary findings were shared with the whole research team in order to check the validity of our analysis, and no contradictory responses were found among the rest of the team.

RESULTS

Reflexive dialogues on ethics played a central role in project design. Many of the project staff came into the first discussion with a narrow focus on their own perspective and their individual piece of the project, and it was not until a variety of opinions were put forth that they realized the ethical implications of the research.

Views of the Research Staff Before Discussion on Ethics

During the planning stages of the project before any of the discussions on ethics, seven of the ten research members had not thought much about informed consent. Most of the researchers who preferred blanket consent were lab scientists primarily involved in animal research. They were in some cases not fully aware of the human subject research protocols, as some noted:

> I just think through our training, actually, the ethics portion is more about, you know, what's ethically correct in publishing your research and not choosing data and things like that, and not necessarily where your samples are coming from…the whole right-to-know is just not addressed. …I deal with the animal side so I knew everything that went into an IACUC [animal protection office] but an IRB was brand new (Lab researcher PS 1).[1]

> I really don't think too much about the ethical issues, I'm focused on the science. I see enough benefits on the other side, therapeutically, that has kind of formed my ethical opinion (Lab researcher PS 8).

These researchers were also not aware that an informed consent process was needed when the study started: "when we started, it didn't occur to me that there would be an informed consent process" (Lab researcher PS 2). Some of the researchers recounted the situations from their past when consent was not needed:

> I'd done research on newborns before and, in those cases we were obtaining cord blood and placentas and now that goes back to the early 1980's, and we didn't ask any of the parents for obtaining those materials, but we consented them all so

[1]Respondents are referred to by these identifiers, signifying "Project staff"

> they'd know about the study and also because we were extracting data from their medical records. … And standards have changed since then. I mean, back then, I am absolutely positive we would have used whatever tissue we wanted with impunity and not talked to anybody. We would've just gone to the pathologists. In fact, I think this would've gone through an expedited review by the IRB (Lab researcher PS 2).

It is common practice in biomedical research to get residual tissues from pathology archives without seeking any consent. Autopsies are done all the time, even with miscarriages and this has been a source to acquire tissues. A team member pointed out that he has been involved in an ongoing project using human fetal testis transplants without consent by just collecting residual tissues from fetuses and deliveries from the pathology archive which had received a blanket consent (lab researcher PS 4). This was verified by one of his colleagues:

> When somebody goes in to the hospital that's gonna give birth at the hospital, whether it's a miscarriage or a real birth, they sign some form--very vague form that says 'my tissue can be used for research purposes.' So, for past couple years, we've received residual tissue" (lab researcher PS 5).

For these researchers involved in tissue procurement, two main arguments came up with regard to using detailed informed consent: one that it would compromise their sample size, and two that they were already under IRB rules, so it was not necessary to do a full informed consent. One researcher felt that discussion on ethics was not necessarily just the main focus, but rather how to get the samples. They thought that it was sufficient to provide blanket consent and perhaps unnecessary to complicate things further by describing the project in great detail to participants, as was the norm in their earlier research work: "I came from that background. [I] thought, you know, the fetus is dead, who cares, let's make use of it the best way we can, why worry about confusing the situation with telling people details about what we're planning to do" (PS4). The emphasis here is that the donated tissue samples will be put to good use for scientific advancement, a public good.

Blanket consent is commonly utilized in biomedical research. It covers all possibilities and allows any use of the material for scientific research at any time in the future. One research staff member defined blanket consent in literally two lines, :I mean you just check yes or no and sign the form, …which gives you zero information… I think they lump fetus, placenta, everything together into one line. … so I'm assuming that's what they're using for a blanket consent form" (PS1). In some cases, blanket consent is sought because the researchers do not have a clear idea of the research protocol, especially in the case of biobanks, but in this study the researchers already have the research protocol in place, which makes it possible to have this discussion on the researchers ethical responsibility towards the participants.

While blanket informed consent is more common in biomedical research, not all the lab scientists were against detailed consent. Three out of the ten research staff were strong supporters of detailed consent. Our scientists who routinely deal with fetal autopsies were less inclined to support detailed informed consent. Our hospital staff who are involved with patient care expected ethical issues to be at the forefront, emphasizing the importance of detailed informed consent for the patient as well as for all family members and other significant persons. Their views were partly formed by working directly with the bereaved patients.

Shifting Tides: Consensus-building on Detailed Informed Consent

The transition from blanket consent to adopting detailed informed consent started with open discussions among project staff on the ethics of fetal tissue research and informed consent. After the initial discussions, most team members agreed to a process of full informed

consent. This expansion of the informed consent beyond the IRB requirement and research norms was attributed largely to reflexive group discussions on ethics:

> I think that what led to the change was just the discussions, and understanding the broader picture - the context of things, I really- I think that's how it evolved. (Lab researcher PS 2).

> I think if you can get a group of people to collaborate like this everything gets done better and you share information, and somebody might know something that you don't and, so for me having the whole group together- I think they already planned on having informed consent. (Lab researcher PS 5).

> It wasn't until everyone came together that you realized sort of the magnitude of what we were doing..and then I flipped. … I walked out of that meeting and went home that night and thought…that blanket consent is really not the best way given what we are going to do with the tissue, the full [detailed] informed consent seemed the appropriate way to go. … I think that a lot of people in my position may not have thought about it the way that we did once the whole group came together (PS1).

The interdisciplinary background of the researchers, spanning medical science and social science, helped broaden these discussions to consider the ethical norms in other disciplines. Team members were able to appreciate the perspective of potential participants who had just experienced a loss. This especially led to pushing the boundaries and designing an approach that is extraordinary in the biomedical field. One team member felt that the full, detailed informed consent process is not terribly innovative, since it is just adhering to principles that people have been talking about for quite a while now. He felt that the novel thing here was that: "We're extending them to an area of research that does not require such an informed consent" (PS2).

This larger discussion on ethical implications personally influenced the team members and some even sought to deepen their awareness and understanding on bioethics on their own, which shows an ongoing development of ethical concerns among the researchers. One of the lab researchers shared that she had been reading *The Immortal Life of Henrietta Lacks*, Rebecca Skloot's (2010) bestselling book on the decades of use of an immortal cancer cell line for which the patient and her family never gave permission. She said that she was "disgusted with scientists and their views" and it made her think about the samples that they are getting, that the sample went far back to a person, and their families, not just to the freezer (PS 1). Needless to say that reflexivity did encourage ethical considerations in the team members, and a thoughtful approach was undertaken for this project, which considered all the different points of view.

In addition to the ethical considerations, media coverage emerged as an important concern. Although blanket consent is legally adequate, team members still believed that details of the project could be misconstrued by the media and result in alarming the public and undermining the science. The team was divided on whether the possibility of a negative response to the animal element necessitated the detailed informed consent or, conversely, warranted a lack of detail so as to not unnecessarily alarm or disturb the patient. Because there is a segment of the population that is fervent about issues surrounding fetal tissue research, members felt it to be important to be aware of this audience and be sensitive and delicate in the presentation of information:

> I think people raising concerns about that or concerns about publishing data and then having the publicity and then having fallout-- potential fallout from that, could have swayed judgment. I think, you know, whenever you're doing science you

> want the science to be good but you also want it to be perceived well, and you don't want to be in the midst of a controversy over how this tissue was obtained and, I think for us especially where it's going to be live, potentially raises more concern in the public than it does if the tissue is taken fixed and just used for pathology or DNA or RNA just because there's a lot of precedence for that and, for us, this is different, its not like someone's donating a piece of an organ to be used to save someone else's life. I think it's…the fact that it's fetal opens up a broader host of concerns for the general public… who owns the tissue?, who has the right to decide? (PS 1)
>
> I have the feeling that if I was living in Texas I might actually feel unsafe being a participant in this research. And I don't feel that way here at all (PS 2).
>
> I know in England there was an instance- and this is several years ago- where a researcher did perfectly legal work with human fetal tissues that ended up being televised in the press for having done what was perfectly legal. But it involved a failure to consent. So the rules changed after that, in England, and became much more restrictive and that-seemed to me, it's important to avoid that kind of notoriety (PS4).
>
> I completely go by my feelings in this case, so this is not about--I don't even know what the ethical code is anymore. I can just imagine what this would look like on the cover of [local newspaper name]--'my child's kidney is in a rat and I didn't know about it' (PS 10).

For some members, doing informed consent was a way to guard against possible negative response, noting the fear of seeing the headline, "My child's kidney is in a rat and I didn't know about it". The project staff also recalled the highly publicized exploitative cases of human tissue use as with decades of use of cancer cell lines from Henrietta Lacks, unapproved genetics research on Havasupai Indians, John Moore, and Hagahai people in the public media. These cases have gained wide popularity and media attention because the patents resulting from research on human genetic material or tissues were sought from the donors without prior informed consent (Skloot 2010; Washington 2011).

Another researcher's views were formed by previous experiences: "And so we always wondered whether this was gonna come back to haunt us- if we were able to publish, are there gonna be moms out there, dads, wondering, 'well was our son's testis [tissues] used in this project and we never approved it?' (PS 5) Another researcher added that "I was struck by how important informing was to some people, which means that's gotta be important to some moms and parents as well. So it was very clear that for some people, it was horrible that we didn't inform [them]" (PS4). The ethical awareness of the public's expectation for transparency was in itself sufficient for ethical responsibility, particularly when tied to highly sensitive topics.

While consensus on detailed consent was reached among the research team members, interviews conducted a year later revealed that four of the research staff still felt that it is unnecessary but supported the majority view, for example: "I'm still not convinced that this should be the way, but since most of the colleagues, I think, believe that-, I'm ok with that. I mean, if most of the colleagues believe that, that's okay" (PS 3). These researchers were focused on the practical concerns to overcome with regards to the study, such as getting a continuous supply of samples to move the research forward. The discussion on blanket consent versus the detailed informed consent displays the classic tension between science and ethics, between the goals of research and the need to do research ethically.

Research Staff Views on Challenges to Detailed Informed Consent

Detailed informed consent, has many practical and logistical concerns. The team members struggled over many details of this consent process on how to communicate the use of fetal tissue, xenotransplantation, the complexity of these scientific concepts, timing of consent, countering the views of the hospital staff who are taking care of the patients and the complexity this adds to the IRB process.

Use of miscarried fetal tissue—Most of the research staff believed that this research presents special and sensitive considerations compared to other research because of the use of miscarried fetal tissue. The team felt it to be emotionally laden and a culturally and politically charged topic, requiring sensitive and delicate handling. Dealing with fetal tissue opened up concerns having to do with sentient life, abortion, religious beliefs, ownership of the tissue, questions over who has the right to decide and, of course, feelings of loss for a child or pregnancy in which much hope may have been placed. A researcher noted:

> Well, there is a strong attachment to a life that you created, that you feel is sacred and shouldn't be manipulated and- that probably you would want some burial for, you know, the tissue. It seems to me that it could be analogous to somebody who wouldn't want to donate their organs to science after they died, you know, they would want a proper burial and, you know, it could be for various reasons- for religious reasons, sort of an honoring of a life that ended that is- basically for that reason (PS 6).

Those who work closely with patients and are involved in the process of miscarriage and loss expressed how emotional it can be, and how parents are very attached to their offspring, fetal or not. This close experience with patients caused some to feel that informed consent is very important, while another believed it was better and kinder to spare the parents who participate in the study from information and potentially alarming details. In addition, because the public holds so many strongly held positions regarding fetuses, some members expected these ethical issues to become a focal point of the research and thus present potential repercussions. A key concern was the fact that the tissue would be biologically functional, which could be an important issue for donors, so they should be aware of that.

Another concern was the importance of explaining to parents that the aim of the study was not to discover the reason for their miscarriage or how to prevent a future loss. One team member felt that parents might likely have "therapeutic misconception" (Applebaum et al. 1987) even though the consent form explicitly states that the research cannot offer answers on why miscarriage happened. Researchers believed that parents want to feel that their loss is contributing to some good, but they must understand that it is not for their own individual good. Three of the six parents that agreed to be interviewed believed that they would get individual results on why they miscarried. This therapeutic misconception might be due to the highly emotional state of mind of the participants, but it might also reflect a shortcoming in the present way of seeking detailed consent. This gave the team important feedback, showing that no matter how clear the informed consent form and its verbal presentation might be, people might still hope for individual causal information. It also provided an opportunity for the team to revisit the detailed consent approach and reaffirm its commitment to detailed consent.

Xenotransplantation—Team members realized that many people believe that animal research is unethical. One researcher put themselves into the potential situation: "this is just not acceptable that a piece of my tissue, my fetus' tissue is alive in a rat and you're going to be manipulating it and doing things that potentially kill that piece… that may flip their decision" (PS 1). The team was divided on whether the possibility of a negative response to

the animal element necessitated the full informed consent or, conversely, warranted a lack of detail so as to not unnecessarily alarm or disturb the parent. One of the team members felt that "you don't need to go any further into the transplantation into a rodent. I felt that was unnecessary… less information about that portion of the study was better. And if they had questions and concerns, then I would go into more detail during the consent process" (PS 9).

Another researcher said that this is an uncomfortable process for even those in the medical profession, and preferred using the term "animal model" rather than rodent, since rodent might cause people to think of negative connotations such as "dirty" or "nasty". (PS 10) Accordingly, the consent form does talk about transplantation into an animal model but does not specify that it is a rodent. Some of the project staff themselves who were not lab scientists had very adverse reaction to rodent transplantation:

> Since I'm not a medical type person, I do have, I think, some aversion to animal studies-so there is sort of a conflict, on the one hand I do feel that the work is meaningful and its not clear that one could actually investigate this kind of science in any other way, so I feel like - its mainly a visceral reaction, rather than being completely informed. …I mean there are people who feel very strongly about, just, any type of animal research and, for them to consent, I think it is kind of deceiving if you're just informing them about the intent rather than the actual procedure, I think that it would be unethical not to have some mention about it. (PS 6)

Several research members commented on how their perspective might change if they were approached as a patient or family member, rather than viewing the issues through a scientist's lens. Opinions varied from not wanting to participate on account of the rodent transplantation, to wanting to participate but not wanting any details about the animal part, to not minding if their tissue was used, even under blanket consent.

Complexity of scientific concepts—Several members believed the research and information to be too complex for participants to understand and, thus thought it unnecessary to go into detail during the consent. One cited the difficulty of forming the language of the consent so that it would be understandable to people of diverse educational backgrounds. However, another member noted that complexity is no excuse for not helping parents who join the study understand it. Team members largely agreed that detailed consent, results or updates provided to parents must be in an understandable format rather than anything too detailed, scientific, or "over the head" for non-science-based people.

Concerns over views of the hospital staff—Many individuals involved in the care of the patients, as well as friends or family members, could influence recruitment success. Most team members thought that the hospital staff would appreciate the provision of detailed informed consent, but were concerned that the project adds more work and more time to their busy schedules and view it as a hindrance in that respect: "they [hospital staff] may feel uncomfortable talking to the parents and saying, there's someone that wants to talk to you about a study… I don't know exactly the logistics of that, but I can see them feeling awkward being put in that position potentially, you know, someone who's obviously grieving and now you're asking for something from them" (PS1).

Researchers were concerned that hospital staff might feel awkward talking to a grieving parents about research, especially if they themselves have qualms with the study. Staff might have concerns as to whether the parents understands the full impact of the study, or issues regarding the fact that the study is not directly benefiting the individual patient. The team remarked that the hospital staff is extremely protective of their patients, so they will be concerned about the emotions involved and whether it is appropriate to increase patient pain by talking about this research. They may be protective of the sensitivity and fragility of the

patients and not look kindly on anything that interferes with patient care and well-being. The staff may be close to the parents with whom they may have bonded, and the natural reaction in a tragic situation is to comfort and support them, not burden them with scientific research. These people could easily advise patients not to take part in the study because of their own beliefs, or even affect a patient's thought process through simple body language, eye-rolling or facial expressions.

Timing of seeking consent—The team realized that the timing of seeking consent was an important factor (Hewitt et al. 2009). For two team members who work closely with the patients, approaching the patient during a sensitive time presented more of an ethical concern than discussing the tissues themselves. One research team member was concerned about the immediacy of having to make that decision by the parents (originally within 18 hours after miscarriage, now 32 hours) during such a vulnerable time: "it's almost like you're having to approach these women as they're in the midst of, their distress, it's like you can't wait until they've been able to process some of their own tragedy, it's almost like you're being forced" (PS 7). Some also pointed out that the need for immediate consent also puts the responsibility to decide solely on the mother, with very little time to consult with other family members, and does not take into consideration the kind of support the participant needs to make the decision (PS 1). If the father was present and involved, it may be appropriate for him to approve of the research as well. Team members spoke of the importance of the potential participant's relationship, support system, and whom she feels she needs to consult on the research decision. In this sense, it is not just about consent but about the parent and her emotional state. The families--or whoever may be present and close to the parents--are likely to be suffering emotionally as well, and may impact the process of seeking consent.

IRB issues—As more specificity in consent was discussed, some feared that there would be less flexibility in the labs' ability to change procedures, as even small changes (i.e. adding another organ system as a target for transplantation) would require the bureaucratic work of an IRB modification, as experienced in the project. Another believed that some researchers might feel resentful that this has set an unnecessary standard and that now they might be hindered in their work if they are not taking this approach.

The Center has worked very closely with the IRB since 2009. The first protocol for the fetal loss study was obtained in October 2009. Since then, the study protocol has been revised a dozen times, sometimes to meet IRB requirements, and other times to make changes or add new sections to the study. Although the IRB approved requested modifications, the process significantly increased paperwork. Even as this article draft was being discussed in a team meeting, a new modification was being planned to expand the number of potential participants by allowing the use of tissues from planned abortions required either to prevent physiological damage to the mother, or due to a severely deformed fetus. While the team initially was opposed to using voluntary abortion tissue due to the potential controversy, broader considerations gave reason for re-evaluation. The fact that the researchers would not profit from the tissues, that the tests would be short-term and the samples would not be kept longer than ten years alleviated some ethical concerns.

Research Staff Views on Overcoming Challenges to Detailed Informed Consent

Emphasis on the purpose of research—The research staff believed that despite the complexities involved in detailed informed consent, it is possible to get study participants interested in this research if they explained the purpose of the research: "If they really got interested in the purpose of the study and saw what was needed then, yeah, they may look at it in a positive light." Members believed that a principle reason a woman may participate in

the study is to feel that her tragedy is contributing towards something good. This could also potentially help parents deal with the emotional loss of a miscarriage. Simply talking about the loss could also help women to process their tragedy or alleviate feelings of guilt. The opportunity to help others may also be viewed as a constructive outlet for their grief. While participation may help some women with their loss, it would be disingenuous to presume that kind of benefit for all participants. Moreover, it should not be considered a justification for doing the study.

Information could reduce prejudices—Team members' felt that more information could only reduce prejudices. They felt that if the complicated medical or scientific concepts were explained correctly in a skillful manner and if the information is not too difficult, then patients might be interested in joining the study. A lab scientist explained that there is nothing bizarre here, that this is not a "Frankensteiny" monster experiment, that it is not about rats so much but the use of rodent as a receptacle, a place where tissue can be viable. It is about the covering on the rat kidney being a convenient place to put the tissue to study the tissue (PS 2), "a box that supports life for a couple of weeks" (PS 8).

Emphasize the benefits of research—Members noted that those who understand science would easily see the medical benefits of the research. A member expressed that it will be hard for women to see the benefits initially, and that it will depend on the team members to explain and convince them of the benefits for the community and the greater good (PS 10). By emphasizing the benefits, they believe that even the complexities in explaining the xenotransplantation could be overcome: "If they are of the belief that most of the things that have made our lives better-drugs and procedures, vaccines, you know, everything has been tested and improved by using rodents, then I don't think it would matter so much to them." (PS 5) Another view was that a specific discussion of the science would lead to the research being seen in a positive light:

> Okay this is gonna lead to something that hasn't begun and you're really gonna be able to look at effects on tissue and maybe that leads to things being, you know, banned…phthalates, pesticides, who knows what we'll wind up looking at or, it may change standards for…exposures for pregnant women and fetuses and really provide data that is just not out there. (PS1)

Another point raised was that "the epigenetic changes induced by environmental toxicants is not well studied" and that it is a valuable piece of science to know about. (PS 2) All members felt that participating could give women a sense of contributing to science. For some, this may be a large benefit and the only reason they need to participate. A few members noted that this area is not well studied and has the potential to be very useful in environmental health, toxicology, and disease prevention, one noting that if donors had a sense of the incomparable value of this tissue, it may help them to see the benefits. To tap such a broad viewpoint on the patient's part, team members felt that the greatest level of detailed consent would help. Some tied this to developing a relationship with an unhurried discussion and a compassionate approach.

Educating the hospital staff—Instructing the staff on how to communicate with patients was considered crucial in gaining their support. This would provide them with an understanding of the importance and purpose of the study, and equip them with tools for properly addressing the concerns of patients that may arise after the research team has left. Sharing the results and successes of the study with the hospital staff was also considered essential for their continued involvement in referring participants. There was also agreement that hospital staff should have an ongoing opportunity to voice concerns, provide feedback and be debriefed.

Implications for Team Members' Future Research

The project staff expressed pride in their approach, believing it to be a positive change for research, for individual patients and for the general public, with potential to impact the ethics of future research in both fetal studies and in research protocols overall. In particular, the team felt that the reflexive ethical considerations in this research were novel and should be shared. One member noted that if we were successful in recruiting women at such a difficult time using full informed consent, this would be a huge contribution, as investigators seem to be afraid of using a detailed consent in other difficult venues.

Most members feel this project and approach has and will continue to affect them, admitting that they would think twice now before using fetal tissues without consent and that their "eyes have been opened" to the emotional aspect behind fetal research. Several also commented that, scientifically, this could affect their future work, allowing an avenue for translational research. If the project is successful and evolves into a long-term study, it could have far-reaching impacts and be a model for similar studies and beneficial for future research on loss and miscarriage.

Most members expected there to be both favorable and unfavorable responses to this ethical approach in the scientific community. One wondered if the group will be criticized for making the research harder and focusing too much on personal responses rather than on getting data. Another believed that some researchers may feel resentful that this has set an unnecessary standard and that now they might be hindered in their work if they are not taking this approach. It was also noted that researchers may not understand, had they not been part of the group discussions, and may just think this group is wasting their time. However, most team members believed very strongly that this project is connected to larger issues surrounding the public's right-to-know and transparency in research, and that in the long term, it helps to build trust and confidence between the scientific community and the public.

DISCUSSION AND CONCLUSION

For the research team, employing reflexive research ethics practice and the decision to provide detailed, rather than blanket informed consent, was very transformative. Reflexive research ethics involves more than simply a concerted discussion of the ethics of the research as it applies to working with participants. The reflexive research ethics process captured all the different phases of planning and deciding on detailed informed consent. It challenged the existing views of the research staff, explored common social beliefs and political views on fetal tissue research, it weighed the staff views on the pros and cons of adopting a transparent process, demonstrated ways to overcome the challenges to adopting a transparent approach, and explored the future implications of adopting a transparent research methodology.

Alternatively, one can argue that though detailed informed consent was the modality used in this research, there was ambivalence among the research staff on if it was essential. Also, one can argue that the shift from blanket consent to a more transparent process may not quite necessarily be due to reflexivity and ethical considerations but may to a large extent be motivated by the sensitive and controversial nature of the topic and how it will be received publicly. The variety of responses or differences on detailed inform consent and the level of information to be provided on the nature of research as obtained from our interviews conducted a year after detailed informed consent was adopted shows that the reflexive research ethics process necessarily did not change research staff's mind or perspectives on research ethics and informed consent, though they agreed to such a modality for this particular research. This lack of unanimity also leaves room to explore alternate ways of

seeking consent. Tiered informed consent is an option that allows more flexibility to the blanket consent process and gives choice to the human subjects on the types of research these biospecimens could be used for or the categories of future use for the donated biospecimen (OHRP 2011, Mascke 2008). But a tiered process still does not require detailing the nature of research. This, we thought was essential in our case as it involved transplantation of fetal tissue into animal models, which is potentially a sensitive matter socially and ethically. Alternatively, provision could be made to provide supplemental information to a tiered or blanket consent for those participates who desire more information as demonstrated in Beskow et al. (2010). The discussion on blanket consent versus the detailed informed consent displays the classic tension between science and ethics, between science and society, between the goals of research and the need to do research responsibly.

Though our researchers had varying views on detailed informed consent, the reflexive research ethics process still challenged the researchers to examine their own understanding and beliefs concerning fetal loss on a personal and professional level. This led to greater sensitivity in interacting with persons outside of the research team, particularly parents who join the study and hospital staff. Reflexive ethical practice also pays attention to how the project would be received by science, public, and governmental audiences. Environmental health and related biomedical research benefits from a continuing process of reflection on ethical concerns. Since our follow-up interviews with study participants showed that half held a misconception that the research would provide information about their own miscarriage, it pressed the team to continually assess their protocol. The team had to question whether they were at all misleading people during the consenting process, or whether the best-intended informed consent was still prone to misunderstanding. Also, people might not understand the term xenotransplantation, since it is sometimes used to describe transplanting animal organs in human bodies for therapeutic purposes. It is conceivable that some people would confuse the two uses of the term and be influenced by the concern over having animal parts in humans, even though that is not part of this research. Reflexive process in this case also aided to conceive of such misconceptions before hand and to present such complex information in the detailed informed consent with better clarity.

Our work demonstrates the delicate nature of this research and the sensitivity that is required when dealing with miscarriage, xenotransplantation, and informed consent. Treating informed consent as an ethical process, rather than a means to an end, was an important aspect of this project. Indeed, choosing to perform detailed informed consent above and beyond what was legally required sends an important message to the community and to science about the prominent role of ethics for this group. The group itself has been strengthened by the ethical approach and if they use this feedback to become self-critical of their own process and improve their methods of research and consent, they will continue to pursue ethical practices in research.

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