Special Article: Ethics and Research

Human duty in fetal loss: A study of fetal research on hematopoiesis

Human response to the death of a loved one varies among different societies, religions, cultures, and races through a series of ceremonies and observances. Since postmortem examination may be offensive to some of these groups, the determination of the need for autopsy should be based on ethical as well as legal principles. Ethics is the (science which treats of human nature and the grounds of moral obligation; the science of human duty). Although it is the responsibility of society and the duty of a medical examiner/coroner to provide medicolegal death investigation, establishing dogmatic policy is apt to create confrontation rather than fulfillment of statutory obligations. The approach to an objection to autopsy should stress values of (respect, compassion, kindness and courtesy beyond the minimum required by any policy or guideline). An ethical dilemma for the death certifier is statutory authority versus family autonomy, which necessitates a balance between societal implications of the death investigation and respect for the family's wishes[1]. The problems consist of satisfying legal requirements in the public interest and the avoidance of needless publicity, litigation, and legislative reactions. Controversy over the autopsy wastes valuable personnel time and effort, which could paralyze a busy day at the office. In addition, it is conceivable that a family might later claim that a medical examiner had a duty to perform an autopsy despite family objection and bring suit on the basis that the family lacked ability to make a sound judgment decision in the matter[2].

The purpose of this paper is to explore some of the implications for this balanced approach to the ethics of fetal research[3]. We do so in terms of the concept of the fetus as a patient, which has become a central concept in obstetric ethics internationally. We begin with an account of this ethical concept and then examine some of its ethical implications for a balanced approach to the ethics of fetal research. The concept of the fetus as a patient is not usefully understood in terms of the independent moral status of the fetus-that is, some features of the fetus that, independent of other entities, including the pregnant woman, physicians, and the state, generate the obligations of others. This is because all attempts to establish such independent moral status are doomed to failure. Put simply, there are irreconcilable differences among philosophic and theologic methods that have been deployed over the centuries of debate about the independent moral status of the fetus[4]. A more fruitful line of argument is that the moral status of the fetus depends on whether it is reliably expected later to archive the relatively unambiguous moral status of becoming a child and, later, the more unambiguous moral status of being a person. The fetus is a patient when reliable links exist between it and its later archiving the moral status as a child and then a person[4].

The first link between a fetus and its later achieving moral status as a child and then a person is being presented to a physician and viability, the ability of the fetus to exist ex utero. This requires levels of technologic support necessary to supplant immature or impaired anatomy and physiology through the neonatal period and into the second year of life, times at which no one disputes that childhood and then adulthood exist. Viability is, therefore, not an intrinsic characteristic of fetus, but a function of both biology and technology. In developed countries, fetal viability occurs at approximately the 24th week of gestational age, as determined by competent and reliable ultrasound dating[5].

The second link between a fetus and its later achieving moral status as a child and then a person is being presented to a physician and the decision of the pregnant woman to continue a previable pregnancy to viability and, subsequently, to term. This is because a previable fetus and its later achieving moral status as a child and then a person is the pregnant woman's autonomy, exercised in the decision not to terminate her pregnancy and to present the fetus (and herself) to the physician, because technologic factors do not exist that can sustain the fetus ex utero.

The viable fetus, when the pregnant woman presents herself for a medical care, is a patient. The previable fetus is a patient solely as a function if the pregnant woman's decision to confer the status on the fetus and present herself for care. When the fetus is a patient, the physician has beneficence-based obligations to protect its life and health[4]. These obligations must be considered along with beneficence-based and autonomy-based obligations to the pregnant woman.

The concept of the fetus as a patient can be used to develop a balanced approach to the ethics of fetal research-that is, an approach that protects the vulnerable fetus, but maintains access of pregnant women to clinical research that might significantly benefit the fetus. The proposed fetal intervention is reliably expected (usually on the basis of previous animal studies) either to be life-saving or to prevent serious and irreversible disease, injury, or handicap for the fetus. Among possible alternative designs, the intervention is designed in a way that involves the least risk of mortality and morbidity to the fetus (which will satisfy the US requirement of minimal risk to the fetus). The mortality risk to the pregnant woman is low, and the risk of diseases, injury, or handicap to the pregnant woman is low or manageable.

The experimental intervention should at least not be more harmful than nonintervention.

Research of hematopoiesis in Down's syndrome diseased fetuses

Samples representing 15 tissue sections of the right lobe of the liver from fetuses with Down's syndrome (DS) and 15 tissue sections of the right lobe of the liver from fetuses from embryos after spontaneous abortion were obtained at 16th, 20th and 24th week of gestation. Livers were cut as thick as 3mm, then fixed in 10% neutral buffered formaldehyde at 4^{o} C for 24 hours and processed for routine paraffin embedding. Paraffin blocks were available in all cases, and tissue sections were stained with hematoxylin-eosin (H-E), PAS, Giemsa and Gomori.

A panel of monoclonal antibodies, all provided by DAKO was applied; particularly, Glycophorin C for the identification of erythropoiesis, Neutrophilic elastase for the granulopoiesis and CD34 for the identification of immature hematopoietic progenitors cells, stromal progenitors cells, and vascular endothelial cells. Five microscopic fields of the parenchyma of the liver were evaluated in each case without knowledge of the clinical data, and the number of stained cells per square millimeter was calculated. The sections were examined independently by two observers, and positive cellular staining for each antibody was manifested as fine red cytoplasmic granularity.

16th week of gestation: The livers of fetuses in both cases (Down's syndrome and those after spontaneous abortion) showed a distinct distribution of hematopoiesis; erythropoiesis mainly occured within the sinuses (averaged 3,820 cells/mm^2, range 2,918 to 4,935 cells/mm^2), and granulopoiesis primarily within the mesenchymal stromal cells of the portal fields (averaged 32 granulopoietic cells/mm^2, range 12 to 75 cells/mm^2). The immunohistochemical control for CD34 to identify the progenitor hematopoietic stem cells showed an intense staining pattern by the endothelial cells of the vessels within the portal fields (averaged 45 CD34 positive cells/mm^2, range 18 to 75 cells/mm^2), while positive expression of CD34 was demonstrated in the stromal cells of the mesenchymal portal tissue (Fig. 1). An inconspicuous number of sinusoids close to the portal triad showed, an immunohistochemical expression of the CD34, by the endothelial cells.

20th week of gestation: At this period of gestation within the hepatic parenchyma in both cases, no significant quantitative increase concerning erythropoiesis and granulopoiesis into the sinuses and portal fields, respectively, was noted. In contrast, in our series of Down's syndrome, a slight increase in the number of CD34 positive endothelial cells of the vessels and in the stromal cells of the mesenchymal portal tissue, was shown ($p< 0.02$) (averaged 66 CD34 positive cells/mm^2, range 48 to 97 cells/mm^2). In addition, a significant number of sinusoids demonstrated an intense expression of CD34 by the endothelial cells.

24th week of gestation: During this period there was no significant quantitative difference concerning erythropoiesis in both settings. In contrast, in our cases of Down's syndrome a much greater portion of the mesenchymal tissues of the portal triads demonstrated granulopoietic activity ($p<0.01$) (the number of granulo-

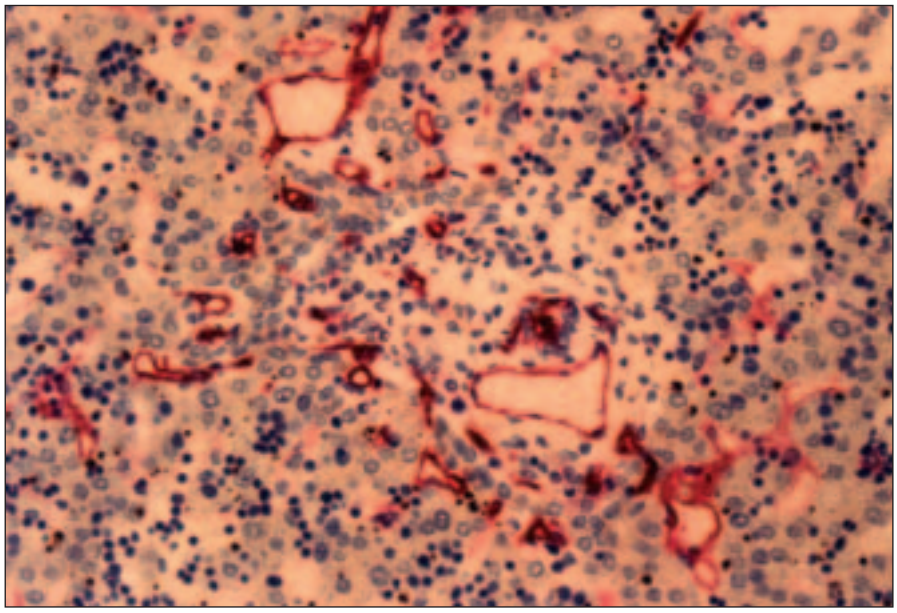

Figure 1. Immunohistochemical control for CD34 showing an intense staining pattern in the progenitor hematopoietic stem cells, progenitor stromal cells and endothelial cells of the vessels. X100 (spontaneous abortion).

poietic cells was more than 2 times higher than those found in spontaneous abortion, averaged 70 granulopoietic cells/mm^2, range 25 to 160 cells/mm^2), while the quantitative expression of CD34 by the endothelial of the vessels within the portal fields was as intense as in the stromal cells of the mesenchymal portal tissue ($p<0.02$) (averaged 105 CD34 positive cells/mm^2, range 58 to180 cells/mm^2) and in the endothelial cells of the extending sinusoids (Fig. 2).

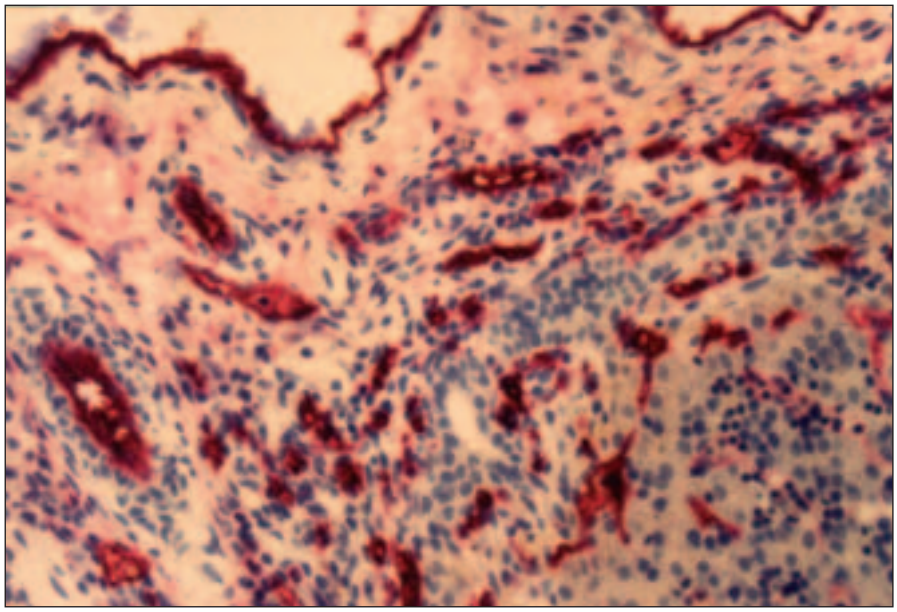

Figure 2. Immunohistochemical control for CD34 showing a strong reactivity with the progenitor hematopoietic stem cells, progenitor stromal cells and endothelial cells of the vessels. X100 (Down's syndrome).

In the United States, federal regulations govern fetal research and are known as 45 CFR 46 or the "Common Rule". All public and private institutions receiving federal funding for clinical research must abide by these regulations. "No pregnant woman may be involved as a subject in an activity covered by this subpart unless: 1) The purpose of the activity is to meet the health needs of the mother, and the fetus will be placed at risk only to the minimum extent necessary to meet such needs; or 2) The risk to the fetus is minimal"[6].

The protective approach to research involving pregnant women reflected in this regulatory language has recently been criticized for being overprotective. This criticism, which has wide-reaching implications for the ethics of human-subject research in all countries, has been made a part of a broader critique of an ethics of human-subject research based almost exclusively on informed consent and protecting vulnerable subjects of research (potential subjects who have diminished capacity to provide informed consent and are, therefore, at risk for exploitation). This critique instigates the argument that the exclusive concern with informed consent-which makes very good sense given the history of abuse of human subjects of research in the United States and in the horrific Nazi medical war crimes earlier-has led to the exclusion of populations of patients from clinical research. As a result, these populations can be denied the benefits of research[7]. For example, it is well known among advocates of women's health that one disturbing outcome of this exclusion of women of childbearing years is that results of studies done exclusively on men must be extrapolated to the clinical care of women[8]. This is obviously not an adequate standard for women's health, especially in developed countries that can afford the cost of clinical research.

Instead of a protective approach, based on the sole ethical consideration of informed consent, a more balanced approach has been recommended. Brody[9] has summarized this emerging, new approach to the ethics of human-subject research. "We are in the midst of a reconceptualization of justice in research, the older conceptualization, the protective conceptualization, emphasized the protection of vulnerable subjects from being used without their consent and from being exploited in excessively risky research. The newer conceptualization, the balancing conception, incorporates access to the benefits of research as an additional demand of justice. As a result, justice in research is now seen as demanding a proper balance of access to the benefits of research with protection from unconsented use and from exploitation". The balanced approach is population-based, whereas the protective approach focuses on individuals.

Conclusions

Fetal research, raises ethical challenges for clinical investigations in maternal-fetal medicine. We have argued for the concept of the fetus as a patient as the conceptual and clinical basis for addressing these ethical challenges regarding the design, conduct, and regulation of fetal research.

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