CONCEPTION to Obtain Hematopoietic Stem Cells

Newborn I,
by Martha Madigan,
1998-99, gold-toned
printing-out-paper
solar photogram,
24" x 20"

Courtesy Michael Rosenfeld Gallery, New York

by JOHN A. ROBERTSON, JEFFREY P. KAHN, AND JOHN E. WAGNER

A couple may have a child to provide stem cells for another child. They may also use preimplantation testing—even, troubling though it is, prenatal testing and selective abortion—to ensure a close tissue match.

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Parents with children who have diseases affecting the blood or immune system often face a difficult dilemma. Hematopoietic stem cells from umbilical cord blood or bone marrow may cure or alleviate their child's disease, but there may be no histocompatible cells available for transplant. Some parents then decide to have another child, hoping that this child will be a suitable match for bone marrow or umbilical cord blood stem cells for the existing child. If a prenatal test for the primary disease is available, they may request prenatal diagnosis, both to make sure that the fetus is not affected by disease and to ascertain whether the second child will be a suitable match for the first. More recently, some couples have used preimplantation genetic diagnosis to allow them to transfer only HLA-matched embryos to the uterus.

Conceiving a child in order to serve as a hematopoietic stem cell donor raises difficult medical, ethical, and legal issues. An overarching ethical issue is whether it is ethically acceptable to conceive a child in part to be an organ or tissue donor for an existing child. If so, ethical and legal questions then arise about the different methods available for testing whether the child will be a suitable stem cell donor. If the parents opt for testing, they must use either prenatal diagnosis followed by selective abortion (if the fetus is not one they want to bring to term), or preimplantation genetic diagnosis and selective transfer of embryos (to ensure that they have a fetus they want to bring to term). Finally, society as a whole must take up questions about whether and how to restrict, regulate, or provide support for these practices.

The Need for Transplants

Hematopoietic stem cell transplants have become the treatment of choice for many malignant and nonmalignant diseases, including leukemia, Hodgkin's disease, sickle cell disease, thalassemia, and congenital hematopoietic disorders such as Fanconi anemia.[1] Unfortunately, it often is not easy to obtain suitable cells.

The best results are obtained when the cells are from sibling donors.[2] Patients who do not have access to cells from a closely matched relative can face a long and often unsuccessful search to find a compatible donor. The National Marrow Donor Program lists 6.5 million names, leaving a roughly one in four hundred chance, depending on the patient's ethnic group, that an unrelated individual will be an acceptable match. Finding a donor is especially hard for people not of Northern European descent because they have a smaller pool from which to draw.[3] If the parents find an unrelated donor, their child still faces serious immunologic risks of infection and graft versus host disease, in which the transplanted white blood cells attack their host.

The use of umbilical cord blood from an unrelated donor has ameliorated some of the problems associated with marrow donation. The HLA matching need not be as precise, for example. Also, the interval between beginning a search and finding a donor is shorter, and the risk of acute and chronic graft versus host disease is lower.[4] There is still a high risk of opportunistic infection, however. Also, because of the smaller quantities of stem cells in the cord blood, the rate of graft failure increases and fewer neutrophils, essential to the immune system, are recovered.[5]

It is these limitations that have led some parents to consider conceiving another child to serve as a stem cell donor. Parents would have a one in four chance of naturally conceiving an HLA-matched child. If the disease for which the transplant is sought is autosomal recessive, as with Fanconi anemia, then there is only a three in sixteen chance of conceiving a child who is both disease free and HLA matched. Prenatal diagnosis can inform parents both whether the fetus has the disease and whether the child will be HLA matched. Preimplantation genetic diagnosis can ensure that only disease free and perfectly matched embryos are transferred to the woman's uterus.[6]

Indeed, the fact that the parents are willing to conceive another child to protect the first suggests that they are highly committed to the well-being of their children, and that they will value the second child for its own sake as well.

Creating a Child

The central ethical issues that arise with conceiving a child to be a hematopoietic stem cell donor concern the child's rights and welfare. Might the interests of the child be compromised for the sake of the existing child? Even if the child's interests are not directly harmed, do the parents and physicians risk violating the Kantian imperative that we treat other persons as ends and never as "mere means"?[7]

The circumstances in which parents face such choices strongly suggest that these concerns can be overcome, however. If the parents were already planning another child, then their existing child's needs may have spurred them to reproduce earlier than they intended, but advancing the reproductive calendar seems to pose little risk to the second child. Nor is the second child likely to be harmed, or have her interests ignored, even if her sibling's needs motivated her conception. The birth of a child creates a powerful bond regardless of the circumstances of conception. Indeed, the fact that the parents are willing to conceive another child to protect the first suggests that they are highly committed to the well-being of their children, and that they will value the second child for its own sake as well.

Because the hematopoietic stem cells will usually be obtained from umbilical cord blood, no physical intrusions on the child to obtain the stem cells need ordinarily occur. In any event, bone marrow donations from infants and minors to siblings have been ethically and legally acceptable for many years. The burdens of bone marrow aspiration are held to be minor enough, given the benefits to the child from having a sibling survive, to fall within the discretion of

parents to have such a procedure done on their child.[8]

Nor should either failure or success in saving the older child affect the welfare of the new child. The children may end up having a very special bond with each other regardless of whether a transplant occurs or succeeds. If a transplant cures the existing child, the second child will have made a huge contribution to household welfare. Yet if the stem cell transplant fails, the second child is not likely to be blamed for an attempt that would have been impossible without its birth. Although the parents will have suffered a grievous loss, they will be left with a healthy second child, who had helped them try to save the first.

Because conceiving a child to provide cord blood donation does not harm or misuse the child, it falls squarely within the parents' discretion to reproduce as they choose.[9] Decisions to have children have long been entwined with narcissistic or utilitarian purposes, from continuing one's lineage to seeking companionship, replacing a dead or dying child, adding additional workers to the household, and providing a "defence 'gainst time's scythe." Although the need for hematopoietic stem cells might make the purposeful nature of most reproduction more transparent than it usually is, aiding an existing child is as valid as many other reasons that motivate people to reproduce. Indeed, it is a choice that doubles the parents' chance of having surviving children, for it may save the life of an older child while enabling another to be born.

A more serious ethical problem would arise if parents sought to have a child *merely* to serve as a stem cell donor, with no intention to rear the child after its birth. This might occur, for example, if they gave the child up for adoption because she was not a good match, or because they had obtained the umbilical cord blood and were not interested in rearing her. Such a crassly instrumental approach would appear to use the child as a "mere means." It also seems to conflict with standard conceptions of the parents' role as involving a commitment to nurture and care for their children.

As objectionable as such an action seems, however, it is not clear that the parents have actually harmed the child, nor that they should legally be stopped from doing so. If the parents had not decided to conceive the child, the child would never have existed, and life as an adopted child is usually as meaningful and fulfilling as other lives.[10] Although we may judge harshly people who embark on reproduction without intending to care for their offspring, the interests of such children have been advanced *once they are born*, for this motivation has enabled them to exist.

Despite such arguments, however, the practice is sufficiently counter to prevailing conceptions of parental commitments that few physicians would be comfortable participating in it, and many might try to discourage it. They should stick to their position even if the couple makes giving the child up for adoption a condition of conception. Further, clinics should find out whether parents are committed to rearing a child conceived to donate stem cells. Although they may not be able to stop the parents from conceiving, and should not necessarily refuse to use hematopoietic stem cells that become available as a result, they can and should discourage the practice.

If parents may ethically conceive a child in order to provide stem cells to an older child, then the question also arises whether they are *obligated* to do so. But this question can be put swiftly to rest. While parents often make sacrifices for their children, they have no legal obligations to provide blood, tissue, or organs for them, much less obligations to have another child for its sake. Nor are they morally obligated to undertake the onerous task of conceiving and gestating a child to obtain cord blood cells for an existing child. The burdens of producing and rearing the new child are substantial, and are not implicitly assumed in the decision to have the first child. These choices are sufficiently personal that they should be left to individual discretion. Likewise, if they have tried once to produce a child with compatible stem cells and have not succeeded, they are not morally or legally obligated to continue trying.

Assuring a Match

There are different methods for assuring a close HLA match, and they raise different issues.

Coital conception followed by gestation without prenatal testing offers the least certainty, for one cannot tell in advance whether the second child will be the one in four that is HLA matched, much less satisfy the three in sixteen chance that the child will be both HLA matched and free of autosomal recessive disease. Of course, it can happen. In the well-publicized Ayala case in 1993, a couple underwent a vasectomy reversal and then gave birth to a naturally conceived daughter who was an exact match for a daughter with chronic myelogenous leukemia.[11] Parents who embark on coital conception for this purpose should understand the relatively low probability of success and commit themselves to rearing a child regardless of the closeness of a match.

Much greater certainty that the child will be a close HLA match is possible with prenatal diagnosis, perhaps followed by selective abortion, and preimplantation genetic diagnosis followed by selective transfer. Each method has advantages and disadvantages.

Prenatal Diagnosis

For many blood disorders, prenatal diagnosis can inform parents both whether a fetus has the disease and, if it does not, whether it would be a close HLA match for the child they already have. If the match is not close, the parents will be better prepared to pursue other therapeutic alternatives.

Alternatively, they could decide to terminate the pregnancy and try again, although most parents in this situation continue the pregnancy to term. Arlene Auerbach, for example, studied thirty-two couples who underwent prenatal testing after conception of a child they hoped would serve as a stem cell donor to an earlier child afflicted with Fanconi anemia. All but two of the twenty-six fetuses that were poor HLA matches were nonetheless carried to term.[12]

The question of abortion is particularly troubling. In theory, parents could even use abortion not only to screen out affected or poorly matched fetuses but even to obtain matched fetal tissue *after* abortion. Those who are pro-life would strongly condemn all of these uses of abortion, of course. Those who are pro-choice might accept the termination of affected fetuses, but they might be more conflicted about the abortion of unaffected fetuses that are not a good HLA match, and they might object outright to obtaining matched fetal tissue after abortion.

Somebody who is pro-choice cannot consistently object to the latter choices on the ground that fetuses have rights or interests in themselves, because they deny that premise in their acceptance of a woman's choice of abortion for unwanted pregnancy. Their objection would appear to rest on symbolic or expressive grounds: that is, they do not want to sanction a practice that treats fetuses as resources to serve the needs of others. They might, for example, think that although previable fetuses are not persons or moral subjects, it is disrespectful of human life generally to create and then destroy a healthy fetus merely because it lacks a genetic trait—HLA-matching genes—useful to another person.[13] Such a view is similar to the reluctance that some have to permit the creation of embryos for research, even though they readily accept research on embryos left over from infertility treatments.

Parents faced with getting compatible tissue to save one of their children might disagree that great symbolic importance should be attached to abortion in these circumstances. If the fetus is too undeveloped to have rights or inherent moral status, and abortion is otherwise generally permissible, then arguably no additional disrespect for human life flows from aborting an otherwise healthy fetus that is not a close HLA match. If the parents are not interested in rearing a child who is a poor HLA match, their lack of interest may be enough to make continuing the pregnancy a great difficulty for them—even though they are willing to rear a child who is a close match. Auerbach has reassuringly shown that few parents in this situation have actually chosen to abort.[14] But it would clearly be within a woman's constitutional rights to abort an unaffected, ill-matched fetus, since motivation is not generally a relevant criterion in limiting reproductive rights.[15]

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The logic of this position would extend even to aborting when the fetus is a good match and sufficient hematopoietic stem cells for transplant could be retrieved from fetal remains. On the pro-choice premises, the parents are not harming or wronging the fetus in either case, since it lacks inherent rights and the abortion is occurring as early as possible prior to viability. If parents are not ready to have another child, conception and abortion to obtain fetal tissue will enable them to obtain the stem cells while avoiding the later stages of pregnancy and the birth of a child they are not prepared to rear. For them, these are sufficiently worthy concerns to outweigh the negative symbolism of aborting in order to obtain fetal tissue for transplant.

Current federal law prohibits this course of action. Aborting for the purpose of obtaining fetal tissue for a designated recipient is a felony punishable by up to five years in prison.[16] This ban may be unconstitutional, however, for it appears to violate a woman's right to decide when to get pregnant and when prior to viability to terminate a pregnancy.[17] If the prohibition did significantly burden a woman's decisions about conception and abortion, then its validity would turn on whether the state's interest in not commodifying women and fetuses, or in maintaining a particular view of respect for life, justifies the infringement of liberty. However, because those interests do not justify state restrictions on abortion in nontransplant cases, they may not justify restrictions on abortion to obtain stem cells for transplant.

Preimplantation Genetic Diagnosis

Preimplantation genetic diagnosis, like prenatal diagnosis, provides advance certainty about whether a child is affected by the disease and would be a good HLA match. Its main advantage is that it provides this information prior to implantation and pregnancy, thus making it possible to select embryos rather than fetuses. Several couples with children with Fanconi anemia and other disorders have sought PGD for this purpose. In one well-publicized case, a family with a child with Fanconi anemia was able to use this technique to give birth to an unaffected, HLA-matched sibling whose cord blood was then used for a stem cell transplant to his older sister.[18] Other couples, however, have not been so suc-

cessful.[19] If PGD proves to be safe, effective, and easily accessible for HLA selection of embryos, it could become the preferred technique for parents in this situation.

The Likelihood of Success. PGD has both practical and ethical disadvantages, however. The practical barriers are its efficacy and cost. For women under thirty-five, in vitro fertilization has a take-home-baby success rate of 30 percent or higher, and the success rate is likely to be higher if the woman is fertile, as she likely would be if she is seeking PGD for stem cell donations.[20] However, couples who undergo IVF and PGD in order to obtain HLA-matched stem cells are likely to face a much lower success rate. Since only 75 percent of oocytes retrieved in a stimulated cycle are successfully fertilized, and only 60 percent of them reach the blastocyst stage in vitro, there would probably be considerably fewer viable embryos that meet the three in sixteen chance of being both an identical match and free of autosomal recessive disease. Since not all such embryos will implant and go to term, a couple using PGD to get matched stem cells might have to undergo several IVF cycles to achieve their goal, if they are successful at all.

Regardless of its success rates, many couples lack access to this technique. Few centers provide PGD for any purpose, much less for HLA matching.[21] In addition, the cost of IVF and PGD is prohibitive for many couples. Since health insurance does not now cover IVF and PGD, only couples who can spend $15,000 to $20,000 per cycle, probably for several cycles, will be able to use this method. Although those who can pay for the opportunity should not be denied it just because others cannot pay for it, ensuring access to IVF and PGD for all those whose children need hematopoietic stem cell transplants remains a problem.

Embryo Status. Because the use of IVF and PGD permits the transfer of only the selected embryos, it also involves the intentional creation of embryos that will not be transferred to the uterus. Positions on this aspect of the procedure reflect differing views of the moral status of embryos and the likelihood that using PGD for HLA matching will lead to using PGD for other nonmedical indications. The issue of the embryo's status is sharpest for those who view embryos as having the same moral status and rights that people have after birth. For example, those who hold strong right-to-life views will object to PGD because of the deliberate nontransfer or destruction of embryos that it entails. Those who think the preimplantation human embryo lacks inherent moral status would be more willing to accept the procedure, and indeed would find it less disrespectful of human life than abortion for the same purpose at a later stage of development.

The creation of unneeded embryos poses a much more difficult question for those who, while believing that embryos have symbolic but not inherent value, do not approve of creating embryos solely for research. Although distinguishing the two cases is difficult, creating embryos that are likely to be discarded is for the parents seeking these transplants a necessary part of a medical intervention, with an intended life-enhancing benefit, and so may be more justifiable than creating embryos for medical research. In addition, permitting the procedure might prevent parents from employing prenatal diagnosis and selective abortion to obtain matched tissue.

It is important to bear in mind that even in basic IVF, as performed to help infertile couples have children, it is common practice to create more embryos than can safely be transferred to the uterus and to store or eventually discard the rest. This practice is accepted by most people (those with right-to-life views excepted) because it serves the important purpose of promoting pregnancy for infertile persons. Although PGD for HLA-matching targets a trait that does not threaten a child's health, it does serve an important, life-affirming social purpose—that of saving the life of a child, reassuring parents that compatible stem cells are available, and preventing abortion. Many couples in this situation would find PGD for HLA selection ethically justified.

The Slippery Slope. Some worry that using this procedure to obtain stem cell transplants makes it easier to use reproductive technology for negative selection or eugenic purposes. When PGD is used to obtain stem cells, embryos would be rejected either because they have a serious genetic disease or because they do not provide a specific HLA match. If unaffected embryos can be created and then excluded because they lack a genotype that makes them useful tissue donors, then embryos could be created and discarded for other utilitarian or preferential reasons—because they are of the wrong gender or have other physical traits that might be ascertainable by PGD. Although PGD operates negatively by screening and exclusion, its use for HLA matching might set a precedent for *positive* alteration and gene targeting, as might occur in germline gene therapy, nuclear transfer cloning, enhancement, or other nonmedical purposes. The fear is that these steps will lead to widespread use of PGD and genetic technology to choose, exclude, or alter genomes of offspring as parents choose.

This slippery slope argument assumes both that future genetic alteration and manipulation will be unmitigatedly horrible, and that accepting the procedure now in question—HLA typing of embryos prior to transfer—will lead inexorably to abusive and uncontrollable genetic engineering of humans, if only by changing attitudes that would make the next step toward genetic engineering easier to take. Both premises are flawed. First, some cases of genetic alteration might turn out to be medically desirable and ethically acceptable; one example might be germline gene therapy to remove genes that cause major congenital malforma-

tions. It is simply too soon to say that all genetic alterations we might someday be able to perform on embryos are so unacceptable that anything that might somehow lead to such practices should be prohibited, whatever its benefits.

Second, even if all positive genetic alteration of embryos were to be deemed unacceptable, those practices could be banned without also stopping otherwise justifiable forms of negative genetic selection, such as screening embryos for HLA-type. Given the clear line between negative selection and positive alteration of embryos, it is not necessary to bar cases of highly beneficial negative selection in order to prevent future positive selection.

Embryonic Stem Cells

An alternative that may someday be available is producing hematopoietic stem cells directly from *embryonic* stem cells, thus avoiding the birth of a child in order to obtain hematopoietic stem cells. This option would require skill in directing embryonic stem cells to produce the hematopoietic stem cells needed, and the ability to ensure that those stem cells are HLA-matched to the recipient.

Although research on turning embryonic stem cells into the replacement cells needed for therapy has just begun, if it were successful, unlimited supplies of hematopoietic stem cells could become available for therapy. The problem of ensuring a close HLA-match may be more daunting, however. Unless libraries of embryonic stem cells corresponding to most HLA types existed, histocompatibile stem cells for the recipient would have to be directly fashioned for each patient.

One way of fashioning them would be through therapeutic cloning. If the transplant recipient's own nuclear DNA were transferred into an enucleated egg from the mother, the resulting embryo would be perfectly histocompatible with the recipient. This method would be fruitless if the disease being treated is inborn and genetic, as is likely the case with many childhood diseases. In those cases, disease would very likely recur.

Another way of producing embryonic stem cells would be to create embryos using the parents' gametes and derive the stem cells only from those with a close HLA-match. This method would entail creating embryos that would not be transferred to the uterus, and would raise many of the same issues as preimplantation genetic diagnosis to obtain HLA-matched stem cells. In this scenario, however, pregnancy and childbirth would not be necessary to realize the intended benefits. Some couples would clearly prefer such an option. There are as yet no laws banning the creation of embryos for use or destruction in therapy.

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Policy and Practice

If the reasoning offered here is sound, a couple may have a child to provide stem cells for another child, and they may also use preimplantation testing to ensure a close tissue match. The use of prenatal testing and abortion is more troubling, but may fall within a woman's rights. Interestingly, a similar conclusion has recently been reached by the Human Fertilisation and Embryology Authority in the United Kingdom, after extensive public consultation.[22]

We close with a few observations about policy and practice. First, it should be clear that, except for the possibility of aborting a fetus to obtain from it tissue for transplant, there are few legal barriers preventing parents and physicians from using prenatal testing and PGD to produce HLA-matched stem cells for transplant. The federal government does not fund PGD for HLA selection, nor any other practices surrounding conception to obtain hematopoietic stem cells for transplant, but public funding restrictions do not prevent private funding of conception, prenatal, and embryo selection practices. Of course, future laws against creating embryos for research or therapeutic purposes, if constitutional, could limit some preimplantation methods for ensuring a close match.

Second, parents are not morally or legally obligated to conceive another child to benefit an existing child. Indeed, parents should go forward with conception to obtain stem cells only if they are prepared to nurture, care for, and love any child they have as a result. If they do decide to have a child to obtain stem cells, they may do so without resorting to prenatal diagnosis or PGD. They may also stop after any unsuccessful IVF cycle for this purpose, or after the birth of a child who was not an appropriate match. Given the relative burdens and benefits of conceiving for donation purposes, the decision to conceive a child to serve as a donor for an existing child is quintessentially an individual one to be made or not as the parents choose.

Third, physicians and patient groups should inform parents of these options for obtaining matched stem cells, so that they may choose what is best for them and their child, includ-

ing where they may receive safe and effective IVF and PGD or prenatal services. Physicians and patient groups should also provide counseling to couples who are considering conception to obtain matched stem cells.

In some instances, the best alternative for parents who have a child with a life-threatening disease may be to conceive another child. The parents' commitment to loving and nurturing the second child is the key factor in determining whether such a decision would be acceptable.

Parents considering this course may also wish to explore options for prenatal and preimplantation testing that will assure that the child is free of autosomal recessive disease and is HLA-matched to the child they already have. Such practices may be controversial, but they will often reflect deep concern for *both* children, and should be available for parents who have no other good therapeutic alternatives.

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