Transplantation of fetal cells and tissue: an overview

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Résumé : Les tissus de foetus pourraient être supérieurs aux tissus de source postnatale pour certains types de greffes, à cause de leur plus grande plasticité et de leur teneur plus élevée en facteurs trophiques divers, de leurs faibles niveaux d'antigènes d'histocompatibilité et de leur résistance aux dommages ischémiques. On greffe des tissus de foetus humain au moins depuis 1922, mais la controverse à ce sujet est tout à fait récente, surtout depuis la publication des résultats de certains essais cliniques mondiaux de greffe de tissus de cerveau de foetus pour traiter le diabète ainsi que des troubles hématopoïétiques. Ces greffes semblent prometteuses quant au traitement futur d'une vaste gamme de troubles neurologiques, endocriniens et autres.

Human fetal tissue has been widely used in medical research and experimental therapies. Research in the last 2 decades has led to substantial progress in applying fetal-tissue transplantation to the treatment of human disease. In this article I will summarize the advantages of fetal tissue for transplantation and describe current and potential applications of fetal-cell and tissue transplantation. I will discuss only the use of tissue from fetal cadavers. The ethical issues concerning fetal-tissue use are complex and important; they deserve separate discussion.

Fetal tissue has several characteristics that may make it superior to adult tissue for transplantation.[1] Fetal cells can often differentiate in response to environmental cues or according to an intrinsic program. This plasticity means that such cells may grow, elongate, migrate and establish functional connections with other cells. Fetal cells may proliferate more rapidly and more often than mature, fully differentiated cells. They may produce high levels of angiogenic and neurotrophic factors, which enhance their ability to grow once they are grafted and may also facilitate regeneration of surrounding host tissues.[2] Histocompatibility antigens are expressed at lower levels in some fetal tissues than in corresponding adult tissue, which makes the fetal tissue less susceptible to rejection. Hematopoietic tissue from an early fetus lacks mature lymphocytes that could recognize and attack the recipient's tissues; hence, use of fetal tissue may prevent graft-versus-host (GVH) disease. Fetal tissue can generally survive at lower oxygen levels than mature tissue, and it is therefore more resistant to ischemic damage during in-vitro manipulation or after transplantation. Fetal cells generally lack long extensions or strong intercellular adhesions; they are thus less subject to injury during excision, dissection and grafting. These characteristics probably explain why fetal cells and tissues survive refrigeration or cryopreservation better than those of adults.[3] In addition, fetal tissue is, in many cases, more readily available than corresponding tissue from children or adults.

Research applications of fetal tissue are well established and relatively commonplace. For example, in-vitro cultures have been used to elucidate biochemical and physiologic processes in normal human development, to study viruses that cause disease, to investigate cancer-induction mechanisms and to produce poliomyelitis and rubella vaccines.[4,5] Use of fetal cells by biotechnology, pharmaceutical and other companies to screen new products for toxicity, teratogenicity or carcinogenicity has been reported,[6,7] but these reports have been difficult to substantiate.

Transplantation of human fetal tissue has generated

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more public interest and controversy than any other use.[7,8,9] In the first reported transplant involving human fetal tissue, in 1922, fetal adrenal tissue was transplanted to treat Addison's disease.[10] Soon thereafter, in 1928, fetal pancreas cells were transplanted in an effort to treat diabetes.[11] Fetal bone marrow was first transplanted in 1957.[12] None of these experiments was successful. However, in the past 20 years, thanks to improved understanding and laboratory techniques, more favourable outcomes have been reported. Table 1 summarizes the main current and potential uses of fetal tissue for transplantation.

Table 1: Current and potential applications of fetal-cell or tissue transplantation

Bone and connective tissue
Reconstructive surgery*
Endocrine tissue
Diabetes mellitus
Liver and thymus tissue
Adjunct to chemotherapy for cancer (i.e., rescue of bone marrow)*
Aplastic anemia
Congenital disorders such as hypoalbuminemia and biliary atresia*
DiGeorge's syndrome
Genetic disorders such as hemophilia, and hepatic storage disorders such as Gaucher's disease, Fabry's disease, Hunter's syndrome, Niemann–Pick disease, fucosidosis, Hurler's syndrome, metachromatic leukodystrophy
Hepatic insufficiency caused by infection with hepatitis B virus or other pathogens*
Leukemia
Severe combined immunodeficiency disease
Thalassemia
Neural tissue
Alzheimer's disease*
Amyotrophic lateral sclerosis*
Demyelinating diseases such as multiple sclerosis*
Epilepsy*
Hereditary ataxia (Friedreich's ataxia)*
Huntington's disease
Korsakoff's syndrome*
Parkinson's disease
Spinal cord injury*
Stroke*
Neuroendocrine tissue
Diabetes insipidus*
Hypothalamic hypogonadism*
Ovarian tissue
Infertility*
Retinal cells
Macular degeneration*
Retinitis pigmentosa*
Skeletal or cardiac muscle
Myopathic conditions, myocardial damage and disease*
Skin
Reconstructive surgery

*To date, studies have involved only animals; no clinical trials have been reported.

Transplantation of fetal pancreatic islet cells

The use of fetal pancreatic tissue for the treatment of diabetes mellitus was suggested by several early investigators, including insulin discoverers Sir Frederick Banting and Charles Herbert Best.[13] Standard insulin-replacement therapy often cannot prevent significant and life-shortening complications, including kidney disease, cardiovascular disease and blindness, which could be prevented by the more precise regulation of glucose levels resulting from transplantation of endocrine pancreas (islets of Langerhans) tissue. Fetal pancreas tissue may be preferable to adult tissue because of its high ratio of endocrine to exocrine tissue and its relative lack of highly antigenic passenger cells, which provoke graft rejection. Use of pancreas tissue before a critical period of exocrine development in the fetus leads to degeneration of exocrine cells, yielding relatively pure endocrine tissue;[14] this reduces the need for the difficult islet-purification procedures used to prepare adult tissue for transplantation.

Reversal of experimental diabetes through transplantation of fetal pancreas tissue was demonstrated in animals in 1974.[15] This finding was subsequently confirmed; it is now generally accepted that human fetal-islet tissue is able to survive, develop and restore normal blood glucose levels in immunodeficient rodents with experimental diabetes.[16–22] On the basis of these observations fetal pancreas allografts in patients with insulin-dependent diabetes mellitus have been attempted since 1977,[16,23] mainly in the former Soviet Union and the People's Republic of China.[24–26] By 1991 over 1500 patients with insulin-dependent diabetes had received transplants of fetal pancreas tissue.[7,27,28] Because of the low mass of islets in a fetus, most clinical transplants have involved pooled islet tissue from as many as 24 fetuses of a gestational age of 16 to 20 weeks.[7] Unfortunately, many of the reports of these procedures lack the details needed for critical evaluation. Of the 1500 graft recipients 16% of recipients showed a measurable increase in serum levels of C peptide, which indicates insulin secretion; however, less than 2% no longer needed insulin injections, when followed up to 45 months after transplantation.[28] The presence of antigenic passenger cells in the transplanted islet tissue may have contributed to this poor success rate. To address the problem of passenger cells, investigators have tried enzymatic treatment and culture of tissue before grafting.[29–31] The ability to type human leukocyte antigens (HLA) in tissue from a fetus of a gestational age of more than 14 weeks[32,33] now allows transplantation of fetal islets in HLA-matched recipients, reducing the problem of rejection. It has been claimed that transplantation with the use of cultured islet cells or potent immunosuppressive medication achieves long-lasting reduction in the patient's insulin requirement.[26] Encapsulation in semipermeable membranes may provide another means of protecting islets from rejection

and permitting free passage of glucose and insulin, without recourse to immunosuppression.[34] In a preliminary clinical trial, encapsulated fetal islets were allografted by intraperitoneal injection in three patients with insulin-dependent diabetes.[35] The patients' insulin requirements were reduced, and there was postoperative evidence that the graft had led to insulin secretion, but these changes persisted less than 6 months.

Transplantation of fetal liver and thymus

The limited supply of histocompatible bone marrow for transplantation may be offset by the availability of fetal liver and thymus tissue. This tissue can provide the life-saving stem cells that are lacking in patients with many hematopoietic disorders.

During fetal development, precursors to hematopoietic stem cells arise in the primitive yolk sac at about the 4th week of gestation. They migrate to the fetal liver by the 6th week and then move to the thymus, spleen and bone marrow.[36] Thus, from 4 to 18 weeks of gestation the fetal liver is a concentrated source of pluripotential hematopoietic stem cells.[37] The immunologic immaturity of the fetal liver makes it a useful source of these stem cells. Lymphocytes, which cause GVH disease, are found in the fetal liver only after the 18th week of gestation.[38] No fatal cases of GVH disease have occurred in patients who received liver hematopoietic stem cells from a fetus of gestatational age of less than 14 weeks.[39,40] However, such grafts would still be rejected by the host if his or her immune system were functional. For this reason fetal liver transplantation has been attempted mainly in patients with nonfunctional immune systems. It has been used for treatment of immunodeficiency disorders, for replacement of bone marrow after administration of antineoplastic drugs or exposure to radiation and for treatment of diseases that can be diagnosed in utero (including inborn errors of metabolism), when the fetal recipient's immune system is also immature.

In 1968 two children with thymic aplasia (DiGeorge's syndrome) were successfully treated through transplantation of fetal thymus tissue.[41,42] This has now become the treatment of choice for this rare condition;[43] it has also been used successfully in conjunction with administration of transfer factor for the treatment of thymic hypoplasia with abnormal immunoglobulin synthesis (Nezelof syndrome).[44] Fetal liver transplantation (with or without fetal thymus) has been used in the treatment of severe combined immunodeficiency disease.[45–50] With recent developments in molecular biologic tools, it is now possible to diagnose this disease and other genetic disorders in utero. Touraine and associates have successfully treated two fetuses (one with severe combined immunodeficiency disease, the other with bare lymphocyte syndrome) by infusion of fetal liver and thymus cells into the umbilical vein.[49] The researchers later reported that these grafts were successful and no GVH disease resulted.[50]

This intrauterine technique was also used to treat thalassemia.[48] Aplastic anemia[51–54] and acute myelogenous and lymphoblastic leukemia[55–57] were also treated successfully with fetal hematopoietic tissue. By 1987 fetal liver transplants had been performed in at least 122 patients with aplastic anemia and in 39 with acute leukemia.[37] Improvement was reported in 54% of the patients with aplastic anemia, but a successful graft could be confirmed in only 3%; the large proportion of patients who recovered after fetal hematopoietic transplantation without evidence of a successful graft suggests that noncellular fetal-derived factors may play a role. In contrast, at least transient engraftment (i.e., survival of grafted cells and their progeny) was demonstrated in 41% of the patients with leukemia; in these patients immunosuppression due to high-dose chemotherapy, irradiation and the disease were probably responsible for a rate of graft rejection lower than that in the patients with aplastic anemia and intact immune systems.

In hepatic storage disorders, the absence of functional enzymes leads to the build-up of unmetabolized substrates and illness; fetal liver cells, transplanted in these patients, may secrete the missing enzyme, which could then be taken up by the host cells, correcting their defective metabolism. Touraine and collaborators[48] and Touraine alone[50] reported fetal hematopoietic tissue transplantation for treatment of inborn errors of metabolism, including Gaucher's disease, Fabry's disease, fucosidosis, Hurler's syndrome, metachromatic leukodystrophy, Hunter's syndrome, glycogenosis, Sanfilippo's syndrome, Morquio syndrome type B and Niemann–Pick disease, in 28 patients, with an overall survival rate of 77%, 1 to 16 years after transplantation. Treatment of Hurler's syndrome by in-utero transplantation of fetal liver cells was also attempted.[58] Transplantation of fetal liver cells was used to correct hepatic insufficiency due to hepatitis B;[59] improvements in the patients' liver function were reported, but no evidence of successful engraftment was given.

Application of fetal liver transplantation could expand to other blood, immune, genetic and hepatic disorders. The restoration of hematopoietic function depleted by anticancer therapy opens a vast range of applications. Such therapy often fails because the dose is limited by the need to avoid complete bone-marrow depression. This limitation could, in principle, be circumvented by the use of fetal hematopoietic-cell transplantation after the administration of high, toxic doses of the antineoplastic agents. Thus, such tissue transplants may be applied to the treatment of diseases such as breast cancer that are among the major causes of death in Canada. Other immunodeficiency disorders, including AIDS, could theoretically be treated by fetal-liver transplantation, although no studies have been started.

Fetal-liver transplantation holds great promise in

the area of gene therapy.[60,61] There are indications that grafted hematopoietic stem cells can restore enzyme levels in lysosomal storage diseases.[48,50,62] As well, transplantation of such cells could be used to correct deficiencies of complement and clotting and other factors, including those causing hemophilia. Because fetal cells are actively dividing, they could be modified with the use of straightforward genetic engineering techniques and their applications for gene therapy thus extended.

Congenital and acquired liver disorders, including hypoalbuminemia, biliary atresia and cholestatic syndromes, may also be amenable to treatment with fetal-liver tissue. Dissociated fetal hepatic tissue may also be transplanted to ectopic sites such as the spleen[63] or incorporated in synthetic "neo-organs"[64] to supply needed liver-derived substances. Such an approach may be valuable in the treatment of hepatic insufficiency caused by alcoholism or viral hepatitis. It was recently found that tolerance to organ allografts can be induced in neonatal mice by transplanting fetal-liver cells from the donor strain;[65] this immunomodulatory effect may make it possible to transplant a wide range of organs in infants.

Transplantation of fetal neural tissue

Transplantation of fetal neural tissue has been undertaken largely to treat Parkinson's disease. Because this disease principally affects a discrete population of cells, the dopamineric neurons of the substantia nigra, it appears to be particularly amenable to such treatment. Initial studies involving rodents revealed substantial improvements when fetal dopaminergic brain tissue was implanted in the corpus striatum of animals with an experimentally induced analogue of parkinsonism;[66-68] similar results were subsequently shown in primates.[69-71] How intracerebral fetal neural grafts restore function is incompletely understood, but there is evidence that they can supply missing neurotransmitters or neuromodulators not only by diffuse release but also by reformation of anatomically appropriate synaptic connections with neurons in the brain of the graft recipient.[8,9] In addition, such grafts may produce growth-stimulating factors, stimulate production of these factors in the brain, influence gene expression and other aspects of metabolism, and serve as conduits for the regeneration of brain pathways.[8,9,72,73]

Results of clinical trials of fetal dopaminergic brain tissue transplantation were first reported in 1988 by investigators in Sweden,[74] Mexico[75] and England.[76] Encouraging results and the absence of major complications have led to the continuation of these trials[77-80] and to the initiation of similar trials in several countries, including Cuba,[81] Spain,[82] the United States[83-86] and Canada.[87] These trials and the implications for application of fetal-tissue transplantation to the treatment of other disorders are chiefly responsible for the upsurge in public attention to, and controversy concerning, the use of tissue from fetal cadavers.

By July 1994 more than 140 patients severely afflicted with Parkinson's disease had been treated by implantation in the corpus striatum of fetal ventral–mesencephalic brain tissue, usually from one to six fetuses of a gestational age of 6 to 12 weeks. Improvement was reported in most cases. However, inadequate documentation and lack of standardization make it difficult to evaluate most of these claims, and even well-documented reports have been criticized.[88,89] Fetal adrenal tissue may also synthesize and secrete dopamine; for this reason fetal adrenal tissue was transplanted in three patients with Parkinson's disease in Mexico.[90] Follow-up results have been disappointing, however, and this procedure has been discontinued.[91]

Clinical trials are under way to use fetal neural-tissue transplantation to treat Huntington's disease, in which the degeneration of striatal neurons, particularly those that use γ-aminobutyric acid as a transmitter substance, causes characteristic dyskinesia and mental deterioration. Studies involving rodents[92-94] and primates[95] have shown that grafts of fetal striatal tissue can survive and provide partial restitution of function in animals with lesions caused by an experimentally induced analogue of Huntington's disease. In the first clinical trial of fetal neural transplantation for treatment of Huntington's disease, involving one patient, slight motor improvement was reported 1 year after surgery.[96]

The results of experiments involving animals suggest that dementia caused by Alzheimer's disease, Parkinson's disease or alcoholism (Korsakoff's syndrome) may also respond to appropriate transplantation of fetal neural tissue. These disorders are characterized by profound degeneration of certain monoaminergic pathways, particularly of the acetylcholine projections from the basal forebrain to the neocortex and the hippocampus,[97-99] which may be correlated with the extent of cognitive deficits.[99,100] Memory impairments due to disruption of acetylcholine projections to the neocortex or the hippocampus have been overcome in rats and monkeys by transplantation of acetylcholine-producing fetal neurons to the depleted brain areas.[101-103] Other animal studies showed that fetal neural transplantation to restore serotonin, another monoamine, also ameliorated memory impairments.[104,105]

Patients with degeneration of spinal motor neurons, in such diseases as amyotrophic lateral sclerosis, and of cerebellar neurons, in hereditary ataxia (Friedreich's ataxia), may also be candidates for treatment by fetal neural transplantation.[106,107] Animal studies have shown that fetal spinal motoneurons, transplanted into the experimentally motoneuron-depleted spinal cord of adult rats, can establish anatomic interaction with the host.[108,109] Fetal cerebellar Purkinje's cells transplanted into the cerebellums of mutant mice with degeneration of Purkinje's cells can re-establish features of normal cerebellar circuitry.[110] However, it has not yet been shown that these grafts can induce recovery of function.

Other neurologic disorders may be amenable to treatment through fetal neural-tissue transplantation. Studies involving animals suggest that such transplantation may be used to treat intractable epilepsy,[111-113] spinal cord injury (possibly in conjunction with substrates permitting long-distance growth, such as peripheral nerve)[114-118] and stroke.[119-121] Certain neuroendocrine disorders, including diabetes insipidus,[122] hypothalamic hypogonadism[123] and pituitary hypothyroidism,[124] have been treated successfully in rodents by transplants of fetal hypothalamic or pituitary tissue. Although current hormone-replacement therapy for these conditions is satisfactory, there may be advantages to the feedback-regulated release of the deficient hormones from transplanted cells. Grafted fetal oligodendrocytes are capable of producing myelin,[125,126] which raises the possibility of remyelination of affected regions in patients with multiple sclerosis or other demyelinating diseases through transplantation of such cells. The effects on function of transplantation of fetal glia have not been shown, and it is unclear whether transplanted oligodendrocytes would be also affected by the disease.

Transplantation of other fetal tissues

Damage and degeneration of the retina have been treated in animals by transplantation of retinal-pigment epithelial cells and strips of the photoreceptor-cell layer.[127,128] Histologic observations reveal that immature cells are more effective than adult cells in rescuing the photoreceptors of the host from degeneration.[129] Transplantation of fetal retinal cells may thus have future application in the treatment of retinitis pigmentosa, macular degeneration and other retinopathy.

Certain myopathic conditions may be improved through fetal-tissue transplantation. In animal models of muscular dystrophy, transplanted myoblasts have fused with degenerating muscle fibres, supplying sufficient numbers of normal genes or gene products to rescue the muscle fibres of the host.[130,131] Although myoblasts from adult donors may be used, fetal tissue may be superior. It has recently been shown that transplanted fetal cardiomyocytes can become functionally integrated with host myocardium,[132] which means it may be possible to repair damaged or diseased heart muscle through transplantation of cells.

Fetal ovaries contain large numbers of immature oocytes which could be used for in-vitro fertilization or transplantation as a treatment of female infertility. Transplantation of immature follicles in mice that have undergone an oophorectomy confers the ability to produce normal offspring after natural mating.[133]

Because of their ability to grow, fetal skin, connective tissue and bone have been considered for use in plastic or reconstructive surgery.[134] Successful construction of a vagina with the use of abdominal skin as well as vaginal and uterine tissue from fetuses of a gestational age of 5 months has been described in two cases of vaginal aplasia with normal ovaries (Mayer–Rokitansky–Küster–Hauser syndrome).[135] The grafts retained their anatomic and functional integrity up to 7 years after transplantation; although the grafts were apparently not HLA-matched to the recipients and the recipients were not immunosuppressed, there was no evidence of rejection.[135,136]

In summary, human fetal-tissue transplantation has been used for the treatment of diabetes, Parkinson's disease and hematopoietic, metabolic and other disorders. Results of many trials have been encouraging. Intense investigation is under way worldwide to improve techniques, assess new applications and find alternative sources of tissue.

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