Human Fetal tissue transplantation in Regenerative Medicine

Introduction:

Fetal tissue transplant is the use of fetal organ/fetal tissue/fetal cells after its aseptic and consented collection from voluntarily consenting mother and the recipient of the tissue/organ, who is suffering from an intractable disease like a refractory neurodegenerative disease like the cases of Parkinsonism not responding to modern scientific treatment. The process, included legal consent (affidavit in court), ethical consent by the Institutional ethical committee and thorough screening of the tissue/organ for HIV(1&2), Hepatitis(B & C), Cytomegalovirus etc for the donor and the recipient. Fetal tissue transplantation first came into prominence during the manufacture of polio vaccines where aborted human fetal cells were used.3 (http://amhistory.si.edu/polio/virusvaccine/history3.htm) Earlier,
human fetal tissue transplantation was limited to spontaneous abortions and also from ectopic pregnancy cases only, however with the concept of birth control, induced fetal abortions came into existence. Abortions may be classified mainly into two groups i. induced and ii. spontaneous. 4 (http://www.msdmanuals.com/professional/gynecology-and-obstetrics/abnormalities-of-pregnancy/spontaneous-abortion) Spontaneous abortion is also known as a miscarriage but induced abortion can be done by an expert physician only after sufficient consent from the mother without jeopardizing her health conditions. Many induced abortions are done on healthy fetuses for birth control and social reasons.

Massive wastage of human research resources

In 2003, nearly 42 million induced abortions happened against 46 million in 1995 and most of them in developing countries. These 46 million aborted fetuses are thrown away in hospital pits and incinerators and treated as a biological trash every year. 1 (http://www.abort73.com/abortion_facts/worldwide_abortion_statistics/)

98% of the abortions, termed as unsafe occur in the developing countries. However, WHO estimates the number of abortions occurring worldwide has stalled between the years 2003 and 2008. Recent statistics from 2008, shows there were 29 abortions per 1000 women aged 15-44 in the developing countries whereas only 24 out of 1000 pregnant women in the developed world. In India hysterotomy and ligation is done in mothers having more than 2 living pregnancies. 2 (http://www.who.int/reproductivehealth/publications/unsafe_abortion/induced_abortion_2012.pdf (Facts on Induced Abortion Worldwide)

History and importance of fetal tissue:

Slowly and progressively the idea for fetal tissue transplantation also started gaining momentum in the scientific and medical community for refractory diseases involving multiple systems. Dr. Curt Feed and his colleagues on November 10, 1988, for the first time in the U.S., implanted human fetal cells into the brain of a 52-year-old Parkinson's disease patient named Don Nelson who showed improvements after 6 months of a follow-up visit. (5), 6 (http://www.nytimes.com/1989/05/02/science/in-careful-test-parkinson-s-patient-shows-gains-after-fetal-cell-implant.html?pagewanted=all) Nobel Laureate Prof. Robert G. Edwards in 1991, for the first time summarized an up to date research on fetal tissue in his book. (7) Since 1999, Bhattacharya et.al with proper legal consent, following all guidelines mentioned earlier, performed HLA randomized freshly collected and screened fetal tissue transplantation from consenting mothers undergoing hysterotomy and ligation in a State Govt Hospital in Calcutta (India). in a series of patients suffering from chronic renal failure, fatty liver, motor neuron disease, Parkinson's Disease, Diabetes, Leukopenia, and arthritis. (8) Such state of the art work for the first time are recorded and updated in a book edited by Prof Niranjan Bhattacharya and Prof Phillip Stubblefield of Boston University, USA. (8)

Fetal tissue transplantation and research is an extremely potential area of regenerative medicine partly because of its superior properties compared to adult tissues and even adult stem cells. Fetal cells have unique properties like faster proliferation and doubling time, good self-renewal and growth properties and can differentiate with respect to any environmental cues. (9) They are hypo antigenic and are not rejected by the host system after transplantation due to several mechanisms in place and a lack of vasculature and hematopoietic system. (9)

Fetal Tissue and its Importance:

In terms of nomenclature, a fetus is normally referred to as all the prenatal stages and the embryo refers to the earliest stages following fertilization of an ovum with the sperm. From each of these tissues, different fetal cell lines can be maintained in vitro. The fetal tissue is rich in different stem cells, stromal cells, and the progenitor cells. Fetal tissues are further hypo antigenic in nature due to the expression of low mRNA transcripts of HLA-G.(10) Roelen et.al showed that MSC's from fetal tissues can have an anti-inflammatory effect.(11) In vitro studies of fetal tissue culture has shown low levels of TNF-alpha and more Th2 cell production. The fetal organs are rich in multipotent stem cells. The fetal kidney, for example, has shown to harbour multipotent stem cells so as in the case of the fetal pancreas, fetal heart, fetal liver, and

brain. (12, 13, 14, 15) Different studies justify that fetal tissues respond to injury in a more rapid manner without the formation of scar or fibrosis. This is due to the fact that fetal tissues are able to develop their own micro niche environment which promotes the synthesis of growth factors and cytokines. (9)

Another important property of fetal tissue transplantation is its hypo antigenicity and absence of graft versus host syndrome as evident from various pre-clinical and clinical studies. This hypo antigenicity can be due to the different stages of immunity the fetus undergoes over the course of its maturation inside the mother's womb. Before, 15 weeks, a fetal tissue is in a pre-immune phase or rather in a pre-HLA state. This pre-HLA condition of the fetal tissues if used before 15 weeks will not be targeted by the host's immune system. (16)

Fetomaternal chimerism and inhibition of graft rejection:

The fetal tissue is hypo antigenic and it might develop accommodation or resistance to the T- cells and antibodies. (17, 18) This phenomenon of accommodation might also contribute towards the activation of the complement pathway and its protection from harmful, toxic cells and cytokines. The presence of complement activation in the fetus during pregnancy has already been proved. (19, 20)

Cryoprotection of the fetus also helps in providing it protection against the toxic attack of the host's immune system. PI3K and heme oxygenase pathway have shown to be implicated in both the process of accommodation and successful fetal survival. (21, 22) During the time of pregnancy, evidence has shown that some maternal T cells can penetrate to the fetus, however, the activities of such T-cells are blocked and suppressed by the trophoblast layer of the fetus.

Fetomaternal chimerism is a well-documented phenomenon during pregnancy where there is some degree of exchange of the cells between the mother and the fetus via the blood-placental barrier. Herzenberg.et al first described the fetal genetic material residing in the maternal peripheral circulation thereby coining the phenomenon as fetomaternal chimerism. (23) Molecular biology techniques using single copy fetal DNA has also enabled sex determination by amplifying the fetal DNA in the maternal peripheral blood. (24,25) This passage of fetal cells from the fetus to the mother can reside in the maternal system for years with the earliest detection at 4-5 weeks of gestation and a steady increase in the maternal blood after 24 weeks with a further decline during postpartum. (26, 27)

Some investigators have proved that fetal cells from the mother can be cleared rapidly due to its small half-life of 16 mins. Further, they have shown that this chimerism can be cleared 100% at postpartum. (28). Still others have shown a persistent presence of the fetal cells in the mother's body over many years even after postpartum. (29)The case of fetal microchimerism has been also observed in the maternal bone marrow mesenchymal stem cell population along with mobilized hematopoietic stem cells. (30, 31) This gradual and selective transfer of fetal cells to the maternal system is thought to possess some immune-modulatory effect on the host system as well. Tolerance like accommodation is another important phenomenon by which the fetal tissue survives pregnancy as well as transplantation inside the host for a long time without any graft versus host syndrome. (32, 33) The fetal develops its own micro niche inside the host tissue by downgrading the molecular antennae responsible for immune recognition and rejection. This behaviour is more or less like the mesenchymal stem cells. (34)

Alternatives of Organ Transplantation

Organ transplantation is suggested to patients when all other methods of treatment for an end stage disease have failed. With scientific developments, the science of organ transplantation has also grown with the incorporation of immunology concepts like HLA nuclear antigen matching, allograft T cell immune rejection, antibody activation and graft versus host disease. (35) To combat immune rejection, immune suppressive drugs containing high doses of corticosteroids, monoclonal or polyclonal antibodies are prescribed. Drug therapies like tacrolimus, mycophenolate mofetil, sirolimus, and mizoribine are used in order to suppress the immune system and avoid rejection of the donor organ. (35) However, there are several limitations to this method. The ease of availability in cases of organ transplantation is extremely arduous even in developed nations with long waiting where often the patient requiring organtransplantation succumbs. In poor countries, a cost is a major factor in affording both organ transplantation and immunosuppressive drugs. (35)

The alternatives to organ transplantation are xeno and cadaveric transplantation. Both are attractive options but also have several limitations like chances of zoogenesis, rejection by the host and long term proper physiological function. These limitations ushered a new field in stem cell and regenerative medicine. Scientists now can use different types of stem cells and progenitor cells to reverse several disease conditions. However, not every type of stem cells is user-friendly like embryonic stem cells due to the amount ethics involved including the propensity of formation of teratomas observed in animal models and chances of rejection. Mesenchymal stem cells for their immunosuppressive capabilities along with hematopoietic stem cells are now an attractive source fortransplantation in regenerative medicine. (36) Many of these are still undergoing clinical trials. However, scientists from Calcutta in 1999 for the first time claimed that using HLA randomized freshly collected specific fetal tissue from abortion after proper consent as per Indian Council Medical Research guidelines, help in reversing several end-stage diseases or chronic

symptoms. Another important advantage of fetal tissue transplantation is that it neither forms teratomas nor rejected by the host's immune system.

Working mechanisms of fetal tissues:

As mentioned above, fetal tissue is hypo antigenic and doesn't exhibit any graft versus host disease. Transplantation of freshly collected fetal tissues has many important properties like the presence of a multipotent niche and their ability to migrate and differentiate under appropriate conditions. (37) This migration of cells from the fetal tissue suggests one of the important properties of cell therapy. Another important advantage of the fetal tissue is due to its less vasculature when compared to other solid organ transplantation, are resistant to hypoxic conditions and can well survive even under stressful and less oxygen conditions. (9) Due to less vasculature, it can also avoid the surveillance of T-cells and other immune complexes to its site thereby evading the body's surveillance system. (16)The extracellular matrix of the fetal tissue consists of integrin & non-integrin receptors, collagenous & non-collagenous molecules along with many other ECM proteins which help in the cell adhesion, migration along with the maintenance of a stem cell micro-environment by integrating these multipotent cells onto the ECM matrix surface. (16) This ECM also provides a support for growth factor deposits and upon activation, proteases help in up-regulation of these growth factors by cleaving the molecules and help them in a controlled release in a site or process specific manner essential for the regenerative process. (38)

Experience of fetal lung tissue transplant:

11 patients, (ages between 26 to 64 years, four male and seven female) voluntarily participated n the HLA randomized fetal lung tissue transplant study.(39) As mentioned earlier here too, all the patients were screened for HIV (1, 2), Hepatitis B and C, liver function test, total blood count, blood biochemistry, urea, creatinine, blood sugar, T3 & T4, C-reactive protein and ECG and other blood parameters. Pulmonary function was performed and the parameters used to assess the lung function were FVC and FEV1. Values between 80% to 120% were considered normal.(39) After getting ethical permission, patient, and donor consent, aborted fetuses were collected from mothers who went hysterotomy and ligation.

These fetal lung tissues were placed at the axilla area (2-3 cm in length and breadth) along with 1% Xylocaine or local anaesthesia. The axilla area was cleanly shaved previously with Betadine and 100% rectified spirit solution before placing the tissue. (39) The place of the axilla was subsequently sutured and no prophylactic antibiotics were prescribed except paracetamol for 2-3 days. (39) After 3 months histology studies were conducted by taking a sample tissue from the axilla. Further observation under a microscope revealed no mononuclear cell or leukocyte invasion, thrombosis or endarteritis. (39) No clinical problems were experienced by the patients also. FEV changes were also observed from a baseline level of 2.4-4.4 range to 3.4-4.6. Similarly forced vital capacity increased to a range of 3.6-4.9 from a baseline of 2.7-4.8 Litres. (39)

This reversal of symptoms is due to remodelling of the lung system through the secretion of surfactant from the specialized fetal lung cells namely Type II Pneumocytes. These are secreted from 2nd trimester onwards in cases of fetal lung. (40) The fetal tissue has a range of connective tissues also which forms the ECM and this ECM also provides a rich environment and source for different stem cells, predominantly epithelial and mesenchymal stem cells, progenitor stem cells which have the capacity to migrate, home and transdifferentiate to the site of injury and secrete cytokines and growth factors essential for repairing any damage. (41, 42. 43)

Fetal Neuronal Tissue transplant for Motor Neuron diseases:

2 patients, (62 years and 45 years) volunteered for the study after informed consent from the donor and the patient along with ethical committee clearance. (44) For the patient aged 65 years, a 2nd trimester or 16 weeks healthy aborted fetus was collected after undergoing hysterotomy and ligation. After proper screening and blood tests, the tissue was placed at the axilla region using 2% xylocaine on 12.03.2004.(44) The patient was advised to continue normal neurological treatment. The patient reported every 6th week without any complications and showed signs of improvement and slow regeneration features through EMG once a month schedule , starting from the 3rd month and continued till the 12th month. However, there was a relapse in the patients' condition in June 2005 suggesting the need for another transplant. The patient in November 2005 further requested for the second set of transplantation.(44)

In the 45-year-old patient, same procedures were followed after obtaining the donor consent from the mother and the patient along with ethical committee clearance. (44) This patient was transplanted with a 14 weeks fetus along with 2% Xylocaine at a heterotopic site that is the axilla.(44) Long term follows up till the 12th month showed improvements, however like the previous case it relapsed again and similarly like the first patient the second patient also insisted on a second fetal tissue transplant. However, the patient was lost to follow-up. (44) EMG reports in both the patients were encouraging which may be due to the transfer of neuro-microenvironmental participation along with stem cells and their growth factors and cytokines. (38)

Fetal tissue transplantation for chronic kidney disease

11 patients, (age 39 to 61 years, 3 male and 6 females) were transplanted with fetal kidney tissue in the axilla region after a donor, patient informed consent and as well as clearance from the ethical committee.

(45) All screening procedures and blood parameters for the safety and assessment of the disease were conducted before the application of the fetal tissue. Patients were not given any antibiotics but were prescribed analgesics. (45) A follow-up study revealed a down staging of the disease as per GFR indication in all the cases starting from the 3rd month. Further fall in urea from baseline of 200 mg in 5 patients was observed between 3rd & 9th month. (45) A similar trend was observed in a case of serum creatinine including both conditions of microalbuminuria and microalbuminuria in all the 9 patients.(45) After 3 months from the time of fetal tissue transplantation, a section of the tissue from the axilla region was analyzed and the micrograph showed absence of mononuclear cell invasion and leukocytic infiltration thereby confirming no GVH disease.(45) The patient showed improvement after transplantation of the HLA randomized fetal kidney possibly due to the participation of the stem cells, fetal progenitor cells and its cytokine and growth factor effect. (38) The presence of Integrin and non Integrin receptors in the ECM of the fetal kidney tissue helped in the control and cellular behaviour of the fetal and stem cells in the form of adhesion, migration, growth, maturation, and transdifferentiation. This whole combination of important cellular factors helped in the reversal of the symptoms of a chronic renal disease. (38)

Spinal and Brain-derived neural tissue transplant for Posttraumatic Quadriplegia

Two case studies of human neuronal fetal tissue transplantation obtained from the fetal brain and spinal cord were also reported by the same group in case of 2 (1 male, 18 years and 1 female, 65 years)post-traumatic quadriplegia patients. (46) The 18-year-old male suffered an accident where his C4-C5 were fractured and were graded as C category on the American Spinal Injury Association or ASIA. Due to poor economic conditions the patient was shifted to a state Govt Hospital. Following donor, patient consent, and ethical committee clearance, the patient was transplanted with a 16 weeks spinal cord fetal tissue collected after hysterotomy and ligation and was applied with 2% Xylocaine in the axilla. (46) The patient was continued on all other supportive drugs and by 6 weeks from the date of fetal tissue transplantation, the patient could walk with the stick. 9 months follow-up showed remarkable improvements and thereafter he attended OPD only when needed. (46)

The second female patient suffering from post-operative quadriplegia due to astrocytoma Grade II was treated with a 16-week fetal brain tissue after obtaining ethical permission and informed consent from the donor and patient. (46) The patient was economically poor and could not afford other treatments and volunteered for this treatment. The patient was graded D in ASIA scale. Within 3 weeks the patient showed remarkable improvements. By the 6th month, the patient was completely free from quadriplegia and started her chemo radiation as per the physician's advice.(46) These positive changes in the two patient cases may be due to the plasticity of fetal neural tissue which can provide cues for proper neural development and axonal regeneration. (46)

Cardiac fetal tissue transplant:

In this study 8 patients were selected for fetal tissue transplant with pre-existing disease load of cardiomyopathy, ischemic heart disease, and diabetes mellitus . However, one patient opted out due to HIV infection. (47) All these patients were transplanted with fetal heart tissues after donor consent. (47) Patient consent and ethical committee clearance were obtained before the application of these fetal cardiac tissues at the axilla. After transplantation, no antibiotics were given although the patients were prescribed paracetamol for 2-3 days.(47)

Post 3 months transplantation fetal tissue transplants were collected from the axilla site for micrographic studies which showed no mononuclear, leukocytic invasion, thrombosis or endarteritis. (47) 10 to 20 % improvements were also noticed in the different cardiac parameters post-fetal tissue transplantation. (47) The group of researchers suggested the possibility of migration of the fetal cardiac progenitor cells into the cardiac region combined with the effect of the residual adult cardiac progenitor cells. These cells helped in a reversal of the symptoms as it is known that fetal cardiac cells can form good endothelial cells but lack the property to form smooth muscle cells which can be compensated by the presence of residual adult progenitor cardiac cells. Synthesis of cytokines and pro-angiogenic growth factors from the fetal cardiac tissue can be also one of the reasons as proposed by the research group. (48)

Fetal liver tissue transplantation in Alcoholic fatty degeneration of the Liver

In another study 13 patients (age between 38-64 years, 9 male and 4 female) were enrolled for the study after ethical clearance; patient and donor informed consent. (49) All these 13 patients had alcoholic steatosis and were treated with a freshly collected aborted fetal liver tissue and were administered in the axilla region with 2% Xylocaine prior application at the axillary site. In a follow-up study, patient's albumin increased from 3.95 gm percent to an average of 4.53 gm percent and albumin increased from 134-399 mg/100 ml in blood to 219.23, 193.54 and 184.23 mg in the 3rd, 6th and 9th month respectively. Micrograph of the partially retrieved tissue also showed no signs of leukocyte or mononuclear cell invasion. (49) Several procedures have been tried or established in order to rectify liver diseases like liver transplantation, hepatocyte cell transplantation, cadaveric transplantation, living donor liver & orthotopic liver transplantation, however, there are several risks associated such as morbidity and mortality, infection,

graft versus host rejection s are present. (49) However with fetal tissue transplantation, safety is not an issue as it can be applied to minimally invasive surgery requiring only local anaesthesia.(49)

Fetal midbrain transplant in Parkinson's disease:

In 2011, researchers from Calcutta published a report of 48 cases where patients suffering from advanced idiopathic Parkinson's disease were transplanted with fetal midbrain. (50) For further histological studies, when patients were requested to give a sample of their transplanted fetal tissue after 1yr,which was refused by the majority thinking that if the fetal tissue is removed they will be suffering again. After proper informed consent, the tissues were retrieved and it was revealed that the graft survived after 10 years from the date of placement of the tissue. (51) A study in some of the few tissues revealed that 5 to 15 g of the transplanted tissues present at the heterotrophic site never caused any GvHD in any of the follow-ups of the patients. The scientists concluded that fetal neuronal tissue can survive in an allo-immune system due to its hypo antigenicity as evident from histopathology studies. Also, there is a possible creation of an own fetal microenvironment important for the fetal cells to survive. (52) No differentiation or abnormal growth was observed in the fetal tissue which suggests the presence of apoptosis in full regulation with the genetic make-up of the cell. A degree of tolerance and accommodation also prevailed in the fetal tissue seen similarly in the case of pregnancy and neoplasm cells. Also, neural progenitor cells rich in fetal tissue helped in the improvement of the condition. (52)Other than improvement in the mental and physical conditions of the patients from Parkinson's, there was also a rise in the haemoglobin content which might be due to the erythropoietin content and its impact on the growing fetal brain.(52, 53)

Adrenal fetal tissue transplant in Arthritis:

In another report, 22 patients suffering from advanced arthritis and graded as per American college of Rheumatology (19) were enrolled in the study using fetal tissue transplant. (54) Before collection of the fetus, the donor gave her written voluntary consent for collection. After due ethical committee clearance and patient informed consent and screened for any disease plus all biological parameter tests to assess the clinical conditions, patients were transplanted with adrenal glands collected from the 20-week fetus at the axilla.(55) In follow-up studies, general well-being of the patients was reported along with the gain in weight and complete restoration of mobility found in 36% of the cases with the rest 64% showing partial recovery was observed. (55)

Fetal Thymus transplant in advanced lymphoma and Leukopenia:

Similarly, the same group of Investigators between 1999 and 2006 collected thymus from consenting donor mothers and transplanted it in seven patients (age between 13 and 64 years, 2 females and 5 males) who were suffering from both Hodgkin's and Non-Hodgkin's Lymphoma after patient informed consent and ethical clearance was provided. Post operation, these patients were prescribed paracetamol for 2 to 3 days.(56) After the transplantation and one-month follow-up, studies revealed the WBC count to be between 24,000 to 42,000/mm3. No GvHd was observed in any of the patients. Histology studies further revealed growth, proliferation and differentiation of the fetal thymus in the hosts. Further, the fetal tissue graft was removed in case of Non-Hodgkin's lymphoma due to the massive increase in the WBC count and the levels were found to return to normal rapidly after the complete removal of the graft. (57)

Pancreatic fetal tissue transplant for diabetes:

16 patients (11 male and 5 females and age range 39 to 72 years) were selected for the study after ethical committee clearance and patient informed consent were obtained. (58) Fetal tissues between 9 to 12 weeks all within the first trimester were collected after the donor informed consent was signed. Patient's history was taken followed with screening for different diseases, blood parameters including HBA1c levels were conducted before the pancreatic fetal tissue was applied. (58) Glycosylated haemoglobin came down from 10.38 to 6.8-9.8 range in 1 month and after 2 months it revealed further lowering of the glycosylated glucose to the 6.3-9.2 range. On the third month the HBA1c levels further came down to 5.4-7.6 range thereby gradually reducing the amount of absolute glucose in the blood. (59) Similarly, the pre-transplant albumin levels observed from 24 hours urine sample also came down to 400-1300 mg range from a baseline of 800-2100 mg. A second follow-up study revealed the reduction to a further 200-900 mg range. None of the patients reported any graft versus host syndrome which was also evident from the histology studies taken after 3 months of fetal tissue transplantation. (58)

Thymic fetal tissue transplant in case of Di George's syndrome

Researchers in 1974 have treated infants with Di George's syndrome successfully with a 12-week fetal thymus tissue collected after obtaining proper consent from the donor, patient and clearance from the ethical committee. (60) Small pieces of fetal thymus were transplanted in abdominal muscles of the infant. After a couple of weeks, the respiratory infection disappeared along with no adverse immunological events. (61) Further within a month the lymphocytes reached a normal level in the peripheral blood circulation and till date, the patient is absolutely normal. Further studies were conducted in additional patients with normal T cell numbers post-fetal thymus transplantation except a small decrease in the T-cell count observed in some of the patients after 5 years. 5 of the patients had a long lasting

beneficial effect of more than 20 years with a restoration of normalcy except one who died of cardiomyopathy. (61, 62,63,64,65, 66, 67, 68)

Potentialities of Fetal tissue in Regenerative Medicine:

Fetal tissues have shown good proliferation and differentiation properties into cartilage-like tissues and can be used in spinal cord regeneration and musculoskeletal engineering. (69, 70) Fetal tissues can be easily collected after ethical committee permission and these tissues can be easily manipulated and expanded in cell culture conditions. These cells can be introduced into collagen and hydrogel scaffolds also as a cell delivery model especially in cases of maxillofacial and autologous bone and soft tissue transplantations. Earlier fetal tissue transplantation in the cases of Parkinson's' disease has been a successful one for the first time as reported by scientists from Calcutta, similarly fetal neuronal cells differentiated into GABA'ergic or DA neuron transplantation is an attractive clinical option. (71) Fetal liver cells along with syngeneic thymic cells have been successfully transplanted in a case of severe combined immunodeficiency (SCID) in a child due to unavailability of identical HLA for bone marrow transplantation. (72, 73, 74). The patient is currently leading a normal life without ever receiving any further treatment. Following year, another female infant with SCID was also rectified and completely cured using fetal tissue transplantation.

Further Harvey Cushing in 1912, stated that in future; pituitary transplantation can be based on growing a functional gland from a fetal or neonatal tissue. (75) Safe applications of fetal liver cell transplantation have already been documented by a group of researchers in a clinical study showing marked responses in patients with the end stage liver disease after transplantation with fetal liver stem cells.
(76) Fetal liver transplantation in seven patients suffering from aplastic anaemia has been also tried where four patients have shown positive results with an increase in CD34 positive cells in the peripheral blood count. (77) None of the cases showed any symptoms of GVHD.

For transplantation in diabetes, replacement of beta cells with beta cells still remains the logical choice. However, the problem with a beta cell in vitro culture is that these cells rapidly tend to lose their identities and dedifferentiates into mesenchymal-like stem cells. (78, 79) Human pancreatic islet cells or islet-derived cells are preferred choices for treating diabetes with transplantation followed by fetal and mesenchymal stem cells. (80) Grafting young ovary in mice has shown to rectify ovulatory cycles. (81) Fetal neuronal tissue transplant in cases of quadriplegia patients was first conducted by a team of scientist from Calcutta in 2004. Scientists have also conducted neuronal fetal cell transplantation in monkeys by culturing these cells under in vitro conditions and then transplanting them. (82, 83)

Ethics:

The rationale behind using fetal tissue transplant is to rejuvenate a damaged or degenerated organ. Current transplantation processes have two main weaknesses like HLA matching and immunosuppressive medication post organ transplantation often leading to suppression of the immune system and higher incidence for the appearance of other malignant diseases. (84) Religious and political views have often undermined the potentialities of fetal tissue research and its clinical applications. Moral questions like whether a woman wants to have a baby or undergo abortion have plagued the area of fetal tissue research for quite some time. (84) Clinicians and researchers do believe that if women have the right to decide whether to have a baby or not, the medical community should also have an equivocal right to decide whether they will be lawfully and legally procuring the aborted fetus for further effective treatment strategies. (84, 85)

According to popular belief, the US government has restricted funding for fetal tissue research due to politics of abortion rather than moral views. (84)Scientists believe that with a number of induced abortions happening each year globally, these discarded fetal tissues can work like the "Holy grail of Medicine" especially in poor countries where the cost of affording treatment for end-stage diseases is extremely high. However, care and caution must be taken so that fetal tissue transplantation in the name of therapeutic benefit for patients with no further treatment options is not abused. Fetal tissue transplantation should be strictly regulated and properly reviewed from time to time with scientific, moral, ethical and clinical justifications so that patients are not exploited for commercial benefits. The first and foremost rule of Bioethics is "Do no Harm and try to do good" and in a case of fetal tissue transplantation it should be followed meticulously and in the right spirit for curing the needy and not for monetary gain.

References:

1. http://www.abort73.com/abortion_facts/worldwide_abortion_statistics/
2. http://www.who.int/reproductivehealth/publications/unsafe_abortion/induced_abortion_2012.pdf (Facts on Induced Abortion Worldwide)
3. http://amhistory.si.edu/polio/virusvaccine/history3.htm
4. http://www.msdmanuals.com/professional/gynecology-and-obstetrics/abnormalities-of-pregnancy/spontaneous-abortion
5. Bindu Panikkar, Natasha Smith, and Phil Brown. Reflexive Research Ethics in Fetal Tissue. Xenotransplantation Research. Account Res. 2012; 19(6): 344–369.

6. http://www.nytimes.com/1989/05/02/science/in-careful-test-parkinson-s-patient-shows-gains-after-fetal-cell-implant.html?pagewanted=all
7. Robert G. Edwards : Editor, Fetal Tissue Transplants in Medicine, Cambridge University Press; 1 edition (Nov. 27, 1992)
8. Niranjan Bhattacharya, Phillip Stubblefield: Editors, Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1.
9. Bhattacharya N. Fetal cell/tissue therapy in adult disease: a new horizon in regenerative medicine. Clin Exp Obstet Gynecol. 2004;31(3):167-73.
10. Weiss ML, Anderson C, Medicetty S, Seshareddy KB, Weiss RJ, VanderWerff I, Troyer D, McIntosh KR. Immune properties of human umbilical cord Wharton's jelly-derived cells. Stem Cells. 2008;26: 2865–74.
11. Roelen DL, van der Mast BJ, isn't Anker PS, Kleijburg C, Eikmans M, van Beelen E, de Groot-Swings GM, Fibbe WE, Kanhai HH, Scherjon SA, Claas FH. Differential immunomodulatory effects of fetal versus maternal multipotent stromal cells. Hum Immunol. 2009;70:16–23.
12. Kobayashi A, Valerius MT, Mugford JW, et al. Six2 defines and regulates a multipotent self-renewing nephron progenitor population throughout mammalian kidney development. Cell Stem Cell. 2008;3:169–81.
13. Herzlinger D, Koseki C, Mikawa T, et al. Metanephric mesenchyme contains multipotent stem cells whose fate is restricted after induction. Development. 1992;114:565–72.
14. Vincent SD, Buckingham ME. How to make a heart: the origin and regulation of cardiac progenitor cells. Curr Top Dev Biol. 2010;90:1–41.
15. Kim SS, Kwak SJ, Han J, et al. Regeneration of kidney tissue using in vitro cultured fetal kidney cells. Exp Mol Med. 2008;40:361–9.
16. Niranjan Bhattacharya, Phillip Stubblefield: Editors, Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 25, Treatment by
Human Fetal Neuronal Tissue Transplant at a Heterotopic Site in the Axilla in Case of Motor Neuron Disease: A report of two cases. Niranjan Bhattacharya, Page No: 315-318.
17. Koch CA, Khalpey ZI, Platt JL. Accommodation: preventing injury in transplantation and disease.J Immunol. 2004;172(9):5143–8.
18. Lynch RJ, Platt JL. Accommodation in organ transplantation.Curr Opin Organ Transplant. 2008;13:165–70.
19. Niranjan Bhattacharya, Phillip Stubblefield: Editors, Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 6, Accommodation and the fetus, Ines Silva , Cody A. Koch , Raymond J. Lynch, and Jeffrey L. Platt, Page no: 79-84.
20. Xu C, Mao D, Holers VM, Palanca B, Cheng AM, Molina H. A critical role for murine complement regulator Crry in fetomaternal tolerance. Science. 2000;287(5452):498–501.
21. Bainbridge SA, Smith GN. HO in pregnancy. Free Radic Biol Med. 2005;38(8):979–88.
22. 45. Riley JK, Carayannopoulos MO, Wyman AH, Chi M, Ratajczak CK, Moley KH. The PI3K/Akt pathway is present and functional in the preimplantation mouse embryo. Dev Biol. 2005;284(2):377–86
23. Herzenberg LA, Bianchi DW, Schroder J, Cann HM, Iverson GM. Fetal cells in the blood of pregnant women: detection and enrichment by fluorescence-activated cell sorting. Proc Natl Acad Sci USA. 1979;76:1453–5.
24. Lo YM, Patel P, Wainscoat JS, Sampietro M, Gillmer MD, Fleming KA. Prenatal sex determination by DNA sample from maternal peripheral blood. Lancet. 1989;2:1363–5.
25. Lo YM, Patel P, Sampietro M, Gillmer MD, Fleming KA, Wainscoat JS. Detection of single-copy fetal DNA sequence from maternal blood. Lancet. 1990;335:1463–4.
26. Thomas MR, Williamson R, Craft I, Yazdani N, Rodeck CH. Y chromosome sequence DNA amplified from peripheral blood of women in early pregnancy. Lancet. 1994;343:413–4.
27. Ariga H, Ohto H, Busch MP, Imamura S, Watson R, Reed W, Lee TH. Kinetics of fetal cellular and cell-free DNA in the maternal circulation during and after pregnancy: implications for noninvasive prenatal diagnosis. Transfusion. 2001;41:1524–30.
28. Lo YMD, Zhang J, Leung TN, Lau TK, Chang AMZ, Hjelm NM. Rapid clearance of fetal DNA from maternal plasma. Am J Hum Genet. 1999;64:218–24.
29. Invernizzi P, Biondi M, Battezzati P, Perego F, Selmi C, Cecchini F, Podda M, Simoni G. Presence of fetal DNA in maternal plasma decades after pregnancy. Hum Genet. 2002;110:587–91
30. Adams KM, Lambert NC, Heimfeld S, Tylee TS, Pang JM, Erickson TD, Nelson JL. Male DNA in female donor apheresis and CD34-enriched products. Blood. 2003;102:3845–57.

31. O'Donoghue K, Chan J, de la Fuente J, Kennea N, Sandison A, Anderson JR, Roberts IA, Fisk NM. Microchimerism in female bone marrow and bone decades after fetal mesenchymal stem cell trafficking in pregnancy. Lancet. 2004;364:179–82.

32. Fan X, Ang A, Pollock-BarZiv SM, Dipchand AI, Ruiz P, Wilson G, Platt JL, West LJ. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. Nat Med. 2004;10(11):1227–33.

33. Nagata H, Ito M, Cai J, Edge A, Platt JL, Fox IJ. Treatment of cirrhosis and liver failure in rats by hepatocyte xenotransplantation. Gastroenterology. 2003;124(2):422–31.

34. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No:2,Fetomaternal cell trafficking: A window into the long-term Health effects of treating Disease with Fetal Cell/Tissue Transplants?, Niranjan Bhattacharya and Phillip Stubblefield, Page No: 15-26.

35. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 1, Alternatives of Human Organ/Tissue Transplantation, Niranjan Bhattacharya, and Phillip Stubblefield, Page No:3-10.

36. 23. Ding Y, Bushell A, Wood KJ. Mesenchymal stem-cell immunosuppressive capabilities: therapeutic implications in islet transplantation,Transplantation. 2010;89 (3):270–3.

37. Zeng XX, Tan KH, Yeo A, Sasajala P, Tan X, Xiao ZC, Dawe G, Rudolph G. Pregnancy-associated progenitor cells differentiate and mature into neurons in the maternal brain. Stem Cells Dev. 2010; 12: 1819–30.

38. Yrjö TK, Emilia K, Vasily S, Wagner HD, Jaakko L, Veli-Matti T, Zygmunt M. Extracellular matrix and tissue regeneration. In: Gustav S, editor. Regenerative medicine. Dordrecht: Springer; 2011. p. 21–80. doi: 10.1007/978-90-481-9075-1_2.Part 1.

39. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 24,Fetal Lung tissue Transplant at a Heterotopic Site in Common Chronic Inflammatory Diseases of the Airway:A Study of 11 Cases. Niranjan Bhattacharya, Page No: 307-310.

40. Mendelson CR, Boggaram V. Hormonal and developmental regulation of pulmonary surfactant synthesis in fetal lung. Baillieres Clin Endocrinol Metab. 1990;4(2): 351–78.

41. Abreu SC, Antunes MA, Maron-Gutierrez T, Cruz FF, Carmo LG, Ornellas DS, Junior HC, Absorber AM, Parra ER, Capelozzi VL, Morales MM, Rocco PR.

42. Effects of bone marrow-derived mononuclear cells on airway and lung parenchyma remodeling in a murine model of chronic allergic inflammation. Respir Physiol Neurobiol. 2011;175(1):153–63.

43. Garage-Kermani M, Phan SH. Molecular mechanisms of and possible treatment strategies for idiopathic pulmonary fibrosis. Curr Pharm Des. 2005;11(30): 3943–71.

44. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 25, Treatment by Human Fetal Neuronal Tissue Transplant at a Heterotopic Site in the Axilla in Case of Motor Neuron Disease: A report of two cases. Niranjan Bhattacharya, Page No: 315-318.

45. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 26,Adjuvant Role of Human Heterotopic Fetal Kidney Tissue Transplant in Reversing the Visible Parameters of Chronic Renal Diseases: A Preliminary Report of 9 Cases. Niranjan Bhattacharya, Page No: 321-329.

46. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 27,Treatment by Human Fetal Neuronal Tissue Transplant from Brain and Spinal Cord at Heterotopic Site in Axilla in Case of Posttraumatic Quadriplegia: A Report of Two Cases Niranjan Bhattacharya, Page No: 333-335.

47. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 29,Human Heterotopic Fetal Cardiac Tissue Transplant in Patients with Varying Degrees of Cardiomyopathy with Ischemic Heart Disease and Diabetes Mellitus: A Report of 7 Cases. Niranjan Bhattacharya, Page No: 347-350.

48. van Vliet P, Smits AM, de Boer TP, Korfage TH, Metz CH, Roccio M, van der Heyden MA, van Veen TA, Sluijter JP, Doevendans PA, Goumans MJ. Foetal and adult cardiomyocyte progenitor cells have different developmental potential. J Cell Mol Med. 2010;14(4):861–70.

49. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 29,Fetal Liver Tissue Transplant in Alcoholic Fatty Degeneration of the Liver: A Study of 13 Cases. Niranjan Bhattacharya, Page No: 339-347.

50. Bhattacharya N. A study and follow-up (1999–2009) of human fetal neurotransplants at a heterotopic site outside the brain in patients of advanced Idiopathic Parkinsonism. In: Bhattacharya N, Stubblefield P, editors. Regenerative medicine using pregnancy-specific biological substances. London: Springer-Verlag Limited;2011. p. 407. doi: 10.1007/978-1-84882-718-9_39.

51. Bhattacharya N, Chhetri MK, Mukherjee KL, Ghosh AB, Samanta BK, Mitra R, Bhattacharya M, Bhattacharya S, Bandopadhyaya T. Can humanfetal cortical brain tissue transplant (up to 20 weeks) sustain its metabolic and oxygen requirements in a heterotopic site outside the brain? A study of 12 volunteers with Parkinson's disease. Clin Exp Obstet Gynecol. 2002; 29(4):259-66.

52. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 30, A Study and Follow-Up (1999–2012) of Fetal Midbrain Tissue Transplant (Iatrogenic Chimera) at a Heterotopic Site in Axilla as a Treatment Support in Cases of Adult Idiopathic Parkinsonism Patients. Niranjan Bhattacharya and Abhijit Chaudhuri, Page No: 357-365.

53. Fahn S, Elton RL. Members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marden CD, Calne D, Goldstein M, editors. Recent developments in Parkinson's disease, vol. 2. Macmillan Healthcare Information: Florham Park; 1987. p. 153–63.

54. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 35 Human Fetal Adrenal Transplant at Heterotopic Site as an Adjuvant for Treatment of Excruciating Pain in Cases of Arthritides .Niranjan Bhattacharya and Abhijit Chaudhuri, Page No: 409-420.

55. Bhattacharya N, Chhetri MK, Mukherjee KL, Das SP, Mukherjee A, Bhattacharya M, Bhattacharya S. Human fetal adrenal transplant: a possible role in relieving intractable pain in advanced rheumatoid arthritis. Clin Exp Obstet Gynecol. 2002;29(3):197-206.

56. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 34 Experience with Human Fetal Thymus Transplantation: In a Heterotopic Site in Patients with Advanced Lymphoma and Leukopenia, Niranjan Bhattacharya. Page No: 397-407.

57. Bhattacharya N, Mukherjee KL, Chettri MK, Banerjee T, Bhattacharya S, Ghosh A, Bhattacharya M. A unique experience with human pre-immune (12 weeks) and hypo-immune (16 weeks) fetal thymus transplant in a vascular subcutaneous axillary fold in patients with advanced cancer: a report of two cases. Eur J Gynaecol Oncol. 2001;22 (4):273-7.

58. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 33 Clinical Improvement After First-Trimester Fetal

59. Whole Pancreas Transplant at a Heterotopic Site in Uncontrolled Diabetes with Varying Degrees of Skin Ulceration of the Leg and Emaciation. Niranjan Bhattacharya. Page No: 385-395.

60. 2. Hong R. Thymus transplantation: facts and fancies in 1975. In: Touraine JL et al., editors. Transplantation and clinical immunology. Villeurbanne: Sep- Editions; 1976. p. 215–21.

61. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 32, Fetal Thymus Transplantation in Di George Syndrome. Jean-Louis Touraine, Page No: 379-383.

62. Touraine JL. Perinatal fetal-cell and gene therapy. Int J Immunopharmacol. 2000;22:1033–40.

63. Cleveland WW, Fogel BS, Brown WT, Kay H. Foetal thymus transplant in a case of DiGeorge syndrome. Lancet. 1968;2:1211–4.

64. August CS, Rosen FS, Miller RM, et al. Implantation of a fetal thymus, restoring immunological competence in a patient with thymus aplasia (DiGeorge's syndrome). Lancet. 1970;2:1210–

65. Gatti RA, Gershanik JJ, Levkoff AH, et al. DiGeorge syndrome associated with combined immunodeficiency. J Pediatr. 1972;81:920–6.

66. Biggar WD, Park BH, Stutman O, et al. Fetal thymus transplantation: experimental and clinical observations. In: Bergsma D, editor. Immunodeficiency in man and animals. Sunderland: Sinauer Ass; 1975.p. 361–6.

67. Jose DG, Barnes G, Rossiter EJ, et al. Reconstitution of cellular immune function in a child with thymic aplasia by fetal thymus grafting. Aust N Z J Med. 1974;4:267–73.

68. Mayumi M, Kimata H, Suehiro Y, et al. DiGeorge syndrome with hypogammaglobulinemia: a patient with excess suppressor T cell activity treated withfetal thymus transplantation. Eur J Pediatr. 1989; 148:518–22.

69. Quintin A, Schizas C, Scaletta C, Jaccoud S, Chapuis- Bernasconi C, Gerber S, Juillerat L, Osterheld MC, Applegate LA, Pioletti DP. Humanfetal spine as a source of cells for intervertebral disc regeneration. J Biol Mol Med. 2009;13:1–12.

70. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 14, Fetal Cell Therapy and Tissue Engineering for Musculoskeletal Tissues, Nathalie Hirt-Burri, and Lee Ann Applegate, Page No: 185-190.

71. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 15, Cell Therapy for Parkinson's Disease, Yasushi Kondo, Tsuyoshi Okuno, Sayaka Asari, and Shin-ichi Muramatsu, Page No: 193-202.

72. Touraine JL. Bone marrow and fetal liver transplantation in immuno-deficiencies and inborn errors of metabolism: lack of significant restriction of T-cell function in long-term chimeras despite HLAmismatch. Immunol Rev. 1983; 1:103–21.

73. O'Reilly RJ, Kapoor N, Kirkpatrick D, et al. Transplantation of hematopoietic cells for lethal congenital immunodeficiencies. In: Wedgwood RJ, Wedgwood RJ, Paul NW, editors. Primary immunodeficiency diseases. The March of Dimes Birth Defects Foundation. New-York: Alan R. Liss; 1983. p. I29–137.

74. Touraine JL. Stem cell transplantation. In: Fisk NM, Moise Jr KJ, editors. Fetal therapy. Cambridge, UK: Cambridge University Press; 1997. p. 317–29.

75. Cushing H. The pituitary body and its disorders, clinical states produced by disorders of the hypophysis cerebri. Philadelphia/London: J.B. Lippincott Company; 1912.

76. Kahn AA, Shaik MV, Parveen N, et al. human fetal liver-derived stem cell transplantation as a supportive modality in the management of end-stage decompensated liver cirrhosis.
Cell Transplant. 2010;19: 409–18.

77. Kansas V, Sood SK, Batra AK, et al. Fetal liver transplantation in aplastic anemia. Acta Haematol.1979;62:128–36.

78. Russ HA, Bar Y, Ravassard P, Efrat S. In vitro proliferation of cells derived from adult human beta-cells revealed by cell-lineage tracing. Diabetes.2008;57(6):1575–83

79. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No: 18, Human Pancreatic Progenitors: Implications for Clinical Transplantation in Diabetes, Mugdha V. Joglekar, and Anandwardhan A. HardikarPage No: 244, Conclusion part.

80. Gershengorn MC, Hardikar AA, Wei C, Geras-Raaka E, Marcus-Samuels B, Raaka BM. Epithelial-to-mesenchymal transition generates proliferative human islet precursor cells. Science, 2004; 306 (5705): 2261–4.

81. Robert G. Edwards : Editor, Fetal Tissue Transplants in Medicine, Cambridge University Press; 1st Edition, Nov. 27, 1992, Chapter No.11,Cell grafting and gene therapy in metabolic diseases, M.Adinolfi, Page no: 285.

82. Robert G. Edwards : Editor, Fetal Tissue Transplants in Medicine, Cambridge University Press; 1st Edition, Nov. 27, 1992, Chapter No.10,Transplantation of ovaries and testes, R.G.Gosden, Page no: 253-259.

83. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No.23 Fetal Neural Tissue Transplantation for Spinal Cord Injury Repair, Sankar Venkatachalam, Page No: 299.

84. Niranjan Bhattacharya, Phillip Stubblefield: Editors,
Human Fetal Tissue Transplantation, Springer-Verlag London, 2013, Edition No.1, Chapter No.37, Of Bioethics, Stem Cells, and Tissue Transplants: Sanjukta Banerji Bhattacharya and Phillip Stubblefield, Page No: 441-448.

85. Robert G. Edwards : Editor, Fetal Tissue Transplants in Medicine, Cambridge University Press; 1st Edition, Nov. 27 1992, Chapter No.13, Law and Ethics of Transplanting fetal tissue,J.K.Polkinghorne, Page no: 323-326.