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Leap into Fetal Surgery; In Utero Placental Mesenchymal Stem Cell Therapy, A Contemporary Approach to Treating Myelomeningocele

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Abstract

Myelomeningocele (MMC), a class of spina bifida is a type of neural tube defect. According to the U.S. Centers for Disease Control and Prevention, each year approximately 1,400 babies born in the United States have spina bifida. The disease manifests with the lack of skin and bone covering the caudal part of the spinal cord. The patient developing such a condition often develops lifelong impaired lower limb mobility accompanied by hydrocephalus, and urinary and bowel incontinence. The available interventions include prenatal and postnatal surgery to fuse the dura. Prenatal surgery performed before 26 weeks of gestation reduces the risk of death or the need for ventriculoperitoneal shunting. It also enhanced results on a comprehensive index for mental and motor function. When compared to postnatal surgery, prenatal surgery reduces the manifestation of several secondary outcomes, including the degree of hindbrain herniation seen in the Chiari II malformation.

Stem cell therapy for MMC on animal models of chick, ovine, and rodents with reported cases 15/63, 15, and 136, respectively, using human Embryonic Stem Cells (hESCs), Neural Stem Cells (NSCs), Mesenchymal Stem Cells (MSCs) showed significant coverage of MMC defect and slight neurogenesis was also observed. With an understanding of medical literature about in-utero regenerative capacity, it is to be appreciated that placental stem cells surgically seeded within a biocompatible scaffold of the cell patches can play a part in alleviating the spinal cord manifestation associated with MMC.

Documented animal studies show that incorporating Placental Mesenchymal Stem Cells in prenatal surgery has reported improved neurogenesis and lower limb mobility. In an ovine myelomeningocele model, the development of in-utero myelomeningocele repair with human Placental Mesenchymal Stem Cells seeded onto an extracellular matrix (PMSC-ECM) enhances motor findings.

The clinical trial for the first stem cell therapy on human subjects known as the "CuRe Trial: Cellular Therapy for In Utero Repair of Myelomeningocele." is expected to be finished by 2030. So far, the cases undergoing treatment have shown significant leg movement and a greater degree of bowel and urinary control. This FDA-approved clinical trial is envisioned to be the future of treating MMC.

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Spina bifida background

Spina bifida, a congenital neural tube defect, occurs due to certain environmental and genetic factors that lead to failure of neural tube closure by the 28th day of embryonic development (1). Though non-fatal, spina bifida may have a massive effect on the quality of life of individuals suffering through it as it may cause lower limb functional disability (2). This defect is one of the most common congenital defects of the central nervous system as every year around 150,000 people are born with spina bifida worldwide(3). Subtypes of this defect depend on to what extent failure in neural tube formation has occurred caudally. The mildest form is Spina Bifida Occulta, where a gap appears in the spine but it remains undiagnosed usually as there are no absolute signs and symptoms associated with it. Whereas, in Meningocele, a fluid sac comes out of the baby's back but doesn't contain the spinal cord or nerve so ordinarily there is little to no nerve injury. However, in the most common and severe form of spina bifida i.e, myelomeningocele, a fluid-filled sac, consisting of the spinal cord along with meninges and nerve membrane herniates through the vertebral defect at the lumbosacral region and causes severe physical impairments (4).

Although symptoms vary from patient to patient, non-communicating hydrocephalus coexisting with hindbrain herniation is the most common association seen in MMC patients. Furthermore, it is commonly observed that patients who have MMC usually have a loss of sensation in their lower extremities and trunk, below the lesion level. Other manifesting symptoms include Chiari II malformation (5), orthopedic conditions (scoliosis, hip problems, and foot deformities), and neurogenic dysfunction. Moreover, impaired bowel and bladder are seen in 97% of MMC patients which leads to urinary and rectal incontinence(6).

Stem cell therapy and the Era of regenerative medicine

Cell-based therapy, as a regenerative medicine technique, is regarded as one of the most promising disciplines in modern science and medicine. Stem cell-based regenerative medicine, which allows healthcare workers to address medical problems which have limited prognoses with the current mode of interventions, has achieved significant advancements. Stem cells are the cutting edge of regenerative medicine owing to their exemplary multi-potency. (7)

One of the undifferentiated, unspecialized cells of the human body that can develop into highly specialized cells is called stem cells. Stem cells were once thought to only be able to develop into adult cells of the same organ. There are numerous examples of stem cells today that can differentiate into diverse cell types, including ectoderm, mesoderm, and endoderm. (8)

The different types of stem cells are: (9)

Mesenchymal Stem Cells (MSCs)

Mesenchymal stem cells (MSCs) are extremely potent and regenerative (10) MSCs are currently isolated from several tissues, including tendon, liver, gastric mucosa, cartilage, placenta, cord blood, and blood plasma (9). MSCs differ in their properties based on their organ of origin (11).

Hematopoietic Stem Cells (HSCs)

Human bone marrow is the most common location for HSC extraction. HSCs have the potential to cause immune problems such as transplant rejection. HSCs, nonetheless, have shown to be a beneficial treatment technique in a range of illnesses including anemia, leukemia, and malignant lymphoma(10).

Embryonic Stem Cells (ESCs)

The first pluripotent cell lines to be developed were the embryonic carcinoma (EC) cell lines that were obtained from the undifferentiated portion of human and murine germ cell tumors. EC cells are not suitable for clinical application, although they have proven to be a very useful model system in the laboratory. Currently, the pre-implantation blastocyst is the established source of ESCs. When the appropriate stimuli are applied, the ability of ESCS cell lines to specialize into multiple mature cell types in culture is one of the most intriguing and significant features. (11)

Embryonic stem cells are obtained from early-stage embryos and have the ability to differentiate into all cell types in the body. Adult stem cells, on the other hand, are found in adult tissues and can differentiate into the specific cell types found in those tissues.

There are two main types of embryonic stem cells: embryonic germ cells and blastomere cells. Embryonic germ cells are derived from the germ cells of early embryos and have the ability to differentiate into all cell types in the body. Blastomere cells, on the other hand, are derived from a single cell in the early-stage blastocyst and have the ability to differentiate into specific cell types in the body.

Induced Pluripotent Stem Cells (iPSCs)

In Human induced pluripotent stem cells (iPSCs), stem cells are produced synthetically. (12). The iPSCs can differentiate into all somatic cell types of the body, similar to human embryonic stem cells(hESCs). In terms of appearance, antigenic characteristics, and behavior, they are very similar to embryonic stem cells (ESCs). iPSCs and ESCs have a similar spherical shape, a big nucleus, little cytoplasm, and comparable growth rates. iPSCs have gene expression and chromatin modification patterns comparable to ESCs, confirming their pluripotency. When transplanted into immunodeficient mice, iPSCs, like ESCs produced from blastocysts, can develop teratomas (tumors comprising tissues from all three germ layers). iPSCs can be implanted into a mouse blastocyst, resulting in the formation of a chimera mouse with cells derived from both the iPSCs and the host blastocyst. iPSCs can contribute to the germ line (the cells that produce eggs or sperm), allowing genetic material to be passed down to future generations. Unlike ESCs, iPSCs are derived from somatic cells in tissues such as the skin, tooth tissue, peripheral blood, and urine. Thus, the creation of iPSCs revealed fewer ethical issues than ESCs and offers the advantage of tailored treatment using the patient's somatic cells with features similar to ESCs(52). Various procedures can be used to generate neurons and cardiomyocytes, which are still subjected to research. (13)

Methods for inducing pluripotency in somatic cells can be classified as integrative or non-integrative. While integrative methods have been utilized for basic research, drug discovery, and disease modeling, non-integrative methods are seen to be safer and more appropriate for cell-based therapeutics (53).To create safe and clinical-grade iPSCs, episomal vectors, a non-integrative method, are routinely used(53).

Stable genetic alteration of iPSCs, on the other hand, may still play a role in treating genetic problems or improving cell characteristics for transplantation. (54)While viruses and integrative approaches are effective at reprogramming, they offer safety problems such as insertional mutagenesis. Small compounds, microRNAs, or metabolites, for example, have lesser effectiveness but are frequently utilized in conjunction with traditional reprogramming agents(53)

Combining approaches or employing alternative non-integrative vectors such as episomal vectors for regenerative purposes can improve reprogramming efficiency while maintaining safety(53). With regard to informed consent before using ipscs, the privacy of both donors and patients must be respected. This is because donated cells carry private information in the form of DNA(54).

The creation of clinical-grade viral vectors is one of the most challenging aspects in creating genetically

modified iPSCs for cell therapy. Producing such vectors under GMP conditions(55) necessitates the use of specialized equipment and facilities, as well as highly experienced and professional workers(56).

Benefits of iPSCs

Umbilical cord blood cells collected from calves after delivery can be converted to iPSCs, which can then be differentiated into lab-grown muscle and fat cells, eliminating the requirement for animal sacrifice(57).

iPSCs, in contrast to ESCs, may be easily generated from a patient's own cells and would not be subjected to immune rejection following autologous transplantation of their germ cell derivatives(58)

As a result, deriving patient-specific gametes (particularly sperm) from iPSCs would establish the groundwork for future successful treatment of male infertility(53).

Stem cell therapy as a modern modality of intervention

Stem cell therapy for neurological disorders

Stem cell therapy has the potential to help alleviate the burden of various conditions. According to the trials that have been published, stem cell therapy promises to be safe and effective(14). Randomized clinical trials (RCTs) are required to assess the efficacy of these therapies. It is anticipated that more clinical studies utilizing NSC-like therapies, particularly those using iPSCs as a source of differentiated cells, would be registered in the future(14)

The use of NSCs in Parkinson's disease, a neurodegenerative condition caused by the gradual loss of dopaminergic neurons, has shown encouraging outcomes. Dopaminergic neural progenitor cells can either be produced in vitro from human ESCs or isolated from the embryonic ventral midbrain iPSC(15)

Stroke leads to a lack of oxygen and nutrients for neurons. (16) NSCs have been shown to be capable of inducing neurogenesis and releasing angiogenic factors to encourage local tissue regeneration in preclinical trials employing NSCs to treat stroke. (17)

The neurological conditions most commonly treated experimentally with umbilical cord blood cells are cerebral palsy and hypoxia ischaemic encephalopathy (HIE). For the treatment of cerebral palsy, umbilical cord blood cells have been used in several researches. (18)

The use of stem cells in surgery

Over the years, there have been increasing efforts to utilize stem cells in various medical fields, including surgery. The use of stem cells in surgery improves patient outcomes, reduce recovery time and enhance healing(59). There are two main types of stem cells that are used in surgery: hESCs and adult stem cells.

In an ongoing clinical trial, a study on pigs demonstrated the safety and effectiveness of delivering a Retinal pigment epithelium (RPE) patch made from embryonic stem cells to their eyes, preserving photoreceptor cells without adverse effects on the retinal structure. The phase 1 human trial investigating a synthetic membrane for delivering human embryonic stem cell-derived RPE to patients with macular degeneration showed successful surgical delivery and sustained growth of the cells in both patients for 12 months.(19).

A the study was conducted to evaluate the ability of bone marrow-derived Mesenchymal stem cells (BM-MSCs) to repair liver tissue damage by acetaminophen in a rat model. The study found that the transplantation of BM-MSCs improved hepatocyte regeneration and repressed liver stress and inflammatory signaling. This demonstrated the potential of these cells for liver repair (20). Studies like

this have demonstrated the potential of embryonic stem cells in the repair of damaged tissues and organs and have paved the way for further research in this field.

A recent clinical trial for diabetic foot gangrene showed that mobilized peripheral blood stem cell transplantation with recombinant human Granulocyte colony-stimulating factor effectively increased blood supply, relieving pain and alleviating cold sensations in the lower extremities of patients with diabetic foot. (21).

The use of stem cells in surgery has many benefits. Firstly, stem cells have the ability to differentiate into the specific cells that are needed to repair damaged tissues and organs, which reduces the risk of complications and improves patient outcomes, as proven above by the results of various studies. Secondly, stem cells can produce cytokines that help to stimulate the healing process, leading to faster and more effective recovery (22). Lastly, stem cells can self-renew, which means that they can continue to produce new cells to replace damaged or dying cells, which is important for long-term repair.

Although there are still some challenges that need to be addressed, such as the potential for ethical concerns and the need for further research, the potential benefits of using stem cells in surgery are numerous.

Available treatment and Fetal surgery for spina bifida

Various pieces of research portray that the neurological manifestation of MMC gets worse with time if medical treatment therein is not provided and a patient might end up with lifelong physical impairment. As per the two-hit hypothesis, the defect in neural tube formation is the major initial cause of MMC manifestation, followed by continual exposure to an amniotic fluid which, therefore, causes further damage to neural tissue. To cure this congenital malformation of the central nervous system i.e. MMC and to prevent the exposed nervous system from infection, surgical treatment ought to be done either within 48 hours of birth postnatally or by the 26^{th} week of gestation prenatally (23).

Before medical progress and advancement, the only treatment available for MMC was postnatal surgery followed by management of MMC-associated symptoms, but in recent years of innovation, the idea of prenatal surgery has been emerging as it's providing promising results(23).

So far, the best treatment option to approach is open prenatal surgery for MMC. The study conducted on an animal model has unveiled the fact that neural tissue damage can be prevented by closing neural pores via prenatal surgery during the intra-uterine phase(6). Historically, 75-80% (5) children had to undergo shunt replacement therapy. However, in a Management of Myelomeningocele Study (MOMS) randomized clinical trial, in which prenatal and postnatal surgery outcomes were compared, it is noted that children who have undergone prenatal surgery showed an improved rate of ventriculoperitoneal shunt placement (40% in the prenatal group and 82% in the postnatal surgery group). Furthermore, It is also showed that 44.8% of children who underwent prenatal surgery were able to walk independently at 30 months of age compared to 23.9% of postnatal surgery cases. Similarly, hindbrain herniation was seen in 64% of cases prenatally in comparison to 96% of cases in postnatal surgery at 12 months of age (24).

One of the other advancements made in open Spina bifida prenatal surgery is fetoscopic surgery. Although it's a less invasive method, the outcomes are not plausible because during the procedure the uterus is insufflated with CO_2, thereby causing fetal acidosis. However, certain other techniques being used in fetoscopic surgery reported satisfactory results.

Gaps and loopholes

Previously, the standard choice of treatment for MMC was via postnatal surgery, which comes with obligatory demand of shunt placement with hindbrain herniation at 12 months and 76.1% of the child was not able to walk independently at 30 months of age, therefore minimizing the success rate of postnatal surgery. To enhance the treatment option available to MMC patients so that they can live a better life, further advancements were made thereby leading to the concept of open prenatal surgery. Even though open prenatal surgery is giving promising results, certain other maternal and neonatal risk factors still need to be considered. According to the MOMC trial, the overall rate of bradycardia seen in fetuses during prenatal surgery was 10%, perinatal death was seen in 3%, and respiratory distress syndrome in 21% of the cases (24).

Additionally, a review report by the Children's Hospital of Philadelphia in 2016 showed the high risk of preterm premature rupture of membranes (PPROM), Chorio-amniotic membrane separation, and low preterm birth weight when surgery was done prenatally(25). Fetal surgery not only possesses a greater risk to the remainder of index pregnancy but it might also lead to complications in future pregnancies as well. It is, therefore, crucial to provide a holistic picture to parents before fetal surgery. Moreover, the major drawback of fetal surgery is that it can only be given to healthy mothers.

Fetoscopic surgery, even though it's a minimally invasive procedure and thought to provide better results than open fetal surgery, a study claims that there are much higher risks associated with fetoscopic surgery. Data acquired from the systemic review of multiple fetoscopic spina bifida repair studies conclude 79% preterm membrane rupture rate along with increased demand for neonatal treatment at the repair site.

Lastly, one of the vital concerns that have been arising is ethical issues regarding the consideration of the fetus as a patient. This concept opens the door to philosophical, legal, and social debate. Conclusively, the aforementioned data therein suggests that further advancements ought to be considered to decrease maternal and fetal morbidity.

The Frontier of Fetal Surgery

Prenatal surgery, also known as fetal surgery, is a surgical intervention performed on a fetus in the uterus, with the aim of treating certain conditions or disorders. The concept of fetal surgery has been around for over a century, with early attempts to perform fetal surgery dating back to the 19th century. However, the first successful fetal surgery was not performed until the 1980s, when Dr. Michael Harrison of the University of California, San Francisco, performed the first open fetal surgery to correct spina bifida, a congenital disorder affecting the spinal cord (26).

Fetal medicine since then has been on the road to continuous evolution. It is marked by some key achievements that should be acknowledged. Some of these milestones include Hysterotomy for fetal vascular access for complete exchange transfusion for Rh disease (led by Liley W.), Diagnostic fetoscopy for obtaining fetal blood samples (Hobbins JC., Mahoney MJ.), Shunt-based fetal repair for Lower Urinary Tract Obstruction (Harrison, Globus, Filly, Jonsen), Fetal lamb model for endoscopic MMC repair (Copeland, Bruner), Open resection of fetal cervical teratoma (Hirose, Farmer), Phase 1 trial of In Utero stem cell transplantation for treatment of fetal alpha thalassemia major (MacKenzie), etc. (26) Since then, fetal surgery has evolved and expanded, with new techniques and approaches being developed to improve outcomes and minimize risks.

Advances in prenatal surgery have enabled the treatment of a wide range of conditions, including congenital heart defects (27), twin-to-twin transfusion syndrome (TTTS)(29), and certain tumors like

sacrococcygeal teratoma(28). For example, fetal surgery for the treatment of TTTS has been shown to significantly improve the survival rate of both twins, and to reduce the risk of morbidity and mortality associated with this condition (29). Moreover, the development of minimally invasive surgical techniques is also reducing the risks associated with fetal surgery. One such example is of using partial amniotic carbon dioxide insufflation (PACI) to overcome the visual limitations of operating within a fluid environment. Based on a human clinical trial, the results assured that in cases where PACI could be instituted successfully, the approach offered far superior visualization of the fetoscopic procedure than would have been possible within the amniotic fluid (30). With continued studies on risks and safety, new doors to approaching fetal surgery can be unlocked.

Bridging stem cell treatment and Fetal Surgery

Stem cell therapy has gained significant attention in recent years as a potential solution for a variety of medical conditions, including those affecting fetuses. The use of stem cells in fetal surgery offers unique opportunities for in-utero treatment of various diseases, including spina bifida, trans amniotic stem cell therapy for congenital diaphragmatic hernia, and congenital heart defects.

Previous clinical trials on animals for stem cell therapy in fetal surgery have reported positive outcomes. A study reported that using trans amniotic stem cell therapy for Congenital diaphragmatic hernia in an animal model showed promising results in lung development (31). Moreover, the results of a case study of fetal spina bifida repair using mesenchymal stem cells (MSCs) in a rat model suggested that prenatal MSC transplantation could treat spinal neuron deficiency in NTDs by the regeneration of neurons and reduce spinal neuron death in the defective spinal cord (32). A study on fetal rhesus monkeys evaluated the potential of in-utero transplantation of fetal hematopoietic stem cells (HSCs) from fetal livers for permanent engraftment as a treatment of congenital hemoglobinopathies. It suggested that fetus-to-fetus HSC transplantation may offer the first effective therapy for a genetic disorder in utero(33).

Although there are hesitations when it comes to incorporating stem cell treatment in fetal surgery, there are studies en route to battle the shortcomings. A case report showed success in utero stem cell transplantation in X-linked severe combined immunodeficiency. It suggests that this procedure may be a treatment option in selected cases, such as fetuses exposed to a significant risk of infectious disease (34). An ongoing clinical trial is investigating the safety of in-utero hematopoietic stem cell transplantation in fetuses with alpha-thalassemia major performed at the time of in-utero transfusion of red blood cells(35). The study currently in Phase 1 is expected to be completed in 2025.

Stem Cell therapy for Myelomeningocele

A severe congenital brain abnormality known as myelomeningocele (MMC) occurs when the neural tube fails to completely close between the third and fourth week of embryonic development. (36) Geographical prevalence of MMC ranges from 0.3 to 59.0 instances per 10,000 births, which is significant. (37)Pregnancy termination, postnatal care, or more recently, fetal surgery are some of the current management options available after prenatal diagnosis, in addition to preventive therapy such as regulated intake of folic acid. (24)However, fetal surgery is not a treatment. (38) When looking at patient outcomes at 30-month-old age, for instance, around half of the in-utero treated patients need clean intermittent catheterization to pass urine and more than half are unable to walk without prosthetics. (39)

Further perinatal procedures, such as the use of stem cells may improve the inadequacies of fetal

surgery. Mesenchymal stem cells (MSCs), in particular, have been used in clinical and animal trials to treat spinal cord injuries. (40)

Stem cell therapy for Myelomeningocele - Animal Models

Chick Embryo Model & Human Embryonic Stem Cells

Lee et al. became the first to adopt a cell-based therapeutic strategy to treat MMC. By intra-amniotic injection of human embryonic stem cells (hESCs) into a surgical chick embryo model of MMC, they investigated the ability of the defect to close. The hESCs were taken from refrigerated human blastocysts and introduced into the amniotic cavity as undifferentiated cells using a glucose phosphate-buffered saline media. The researchers demonstrated that the hESCs group's MMC defect lengths were diminished when compared to the controls. However, there were no studies to back up this theory. They proposed that the paracrine activity of the cell and the mechanical bridging effect were the hESCs strategies to promote MMC closure. (41)

Ovine Model & Neural Stem Cells (NSCs)

Neural stem cells (NSCs) were first used in an ovine model by Fauza et al. (42). An L1-L5 lesion was surgically made to evaluate the NSCs directly injected into the spinal cord, in conjunction with its covering with a cellular human dermal patch (43) After a spontaneous vaginal birth, the surviving lambs underwent a functional evaluation, which revealed no significant decrease in paraparesis. The use of NSCs and a human dermal patch showed no significant effect. An immunohistochemistry study revealed that the NSCs had been successfully engrafted in the spinal cord, but the cells remained undifferentiated. It was also discovered that both the grafted NSCs and host cells produced neurotrophic factors, such as glial cell line-derived neurotrophic factor and brain-derived neurotrophic factor, which were found in the cytoplasm of the grafted cells and the extracellular matrix surrounding the host cells.

In an MMC rodent model, the same team worked with rats' NSCs.On embryonic day 10, a single intragastric retinoic acid dose chemically induced the MMC. Amniotic fluid from the dam was used to extract NSCs.On embryonic day 17, they introduced NScs into the amniotic fluid. NSCs maintained an undifferentiated form and were found mainly on vulnerable neural surfaces at embryonic day 21, according to their observations. Using another model, they verified the viability of intra-amniotic injection of stem cells to repair MMC. (42)

Rat Model & Human Amniotic Fluid Stem Cells (hAFSCs)

In the retinoic acid-induced rat model at embryonic day 17, Abe et al. experimented with intra-amniotic injections of xenologous human amniotic fluid CD117-positive stem cells (hAFSCs). Their findings demonstrated that treatment with hAFSCs encourages skin coverage of the cutaneous defect. Additionally, the authors found significantly more tubulin ß-III in the spinal cords of the hAFSCs group, which might be related to enhanced neurogenesis in the MMC lesion. (44)

Chick Embryo & Human Bone Marrow Stem Cell Line

Do-Hun Lee investigated the ability of a human bone marrow stem cell line (B10) and a neural stem cell line (F3) to promote reclosure in spinal open neural tube defects (ONTDs) in chick embryos at Hamburger and Hamilton stage 18 or 19. For each of the four groups—the untreated control, F3, B10, and HFF-1 (human foreskin fibroblast), chick embryos that made it through the process were retrieved. The control group's embryos underwent ONTD surgery but received no cell injection. At 3, 5, and 7 days following injection, HFF (human foreskin fibroblast) groups and the B10 group demonstrated improved reclosure. ONTDs were not covered by F3 cells. When exposed to chick amniotic fluid in

vitro for 48 hours, the cell survival of F3 cells was considerably lower than that of B10 cells. The outcomes demonstrated that B10 cells, not direct cell integration, but rather covering and preserving brain tissues, improve the reclosure of ONTDs. Since F3 cells do not survive well in the amniotic fluid, there may be a connection between this and the F3 group's lack of reclosure capacity. (41)

A potential winner: Mesenchymal stem cell?

To upgrade functional outcomes for individuals with congenital abnormalities, research is being produced to tap the potential of mesenchymal stem cells (MSCs) in promoting prenatal healing. (45). The ability of MSCs to release paracrine substances is thought to be a major element in their therapeutic efficacy, even though the underlying mechanism of action of MSCs is not completely established. (46) Human tissues such as bone marrow, adipose tissue, skin, placenta, and amniotic fluid can all be used to extract MSCs. (47),(48) Due to their improved immunomodulatory and neuroprotective capabilities, placental mesenchymal stem cells (PMSCs) are particularly appealing for the treatment of neurological diseases such as myelomeningocele (MMC) (49),(50). For the prenatal therapy of congenital diseases, PMSCs can be acquired from chorionic villi, which can be retrieved by chorionic villus sampling during early pregnancy. (51). In the widely accepted ovine model, using PMSCs from early gestation during prenatal repair of MMC frequently results in improved hindlimb function postnatally (18*).* Diana Farmer conducted a research study where they found that the density of PMSCs used for patch repair in utero of ovine MMC has an impact on the preservation of the spinal cord, gray matter, and large neurons. Higher PMSC densities led to the increased cross-sectional area of the spinal cord and gray matter, as well as a greater density of large neurons. The best preservation was observed in the group treated with medium-density PMSCs, while the highest density of large neurons was found in the high-density group. The preservation of large neurons is strongly correlated with functional outcomes. PMSCs show promise for fetal repair and improved postnatal locomotor function in spinal cord injury in humans. (49)

CuRe Trial: Cellular Therapy for In Utero Repair of Myelomeningocele

Diana Lee Farmer is conducting a clinical trial (NCT04652908) with primary outcome measures that assess the safety of the placenta-derived mesenchymal stem cell loaded on an extracellular matrix (PMSC-ECM) Product. The intervention includes the use of sonographic supervision. Under sonographic supervision, the initial uterine entry will be made using a uterine stapling device or something similar, just like in the present conventional fetal surgery. The fetus will receive a paralyzing and painkiller intramuscular injection. Under magnification, the myelomeningocele will be closed systematically. The spinal cord will be separated from the surrounding tissue and allowed to fall into the spinal canal, much like in a typical prenatal operation. Next, the PMSC ECM component will be sized to the spinal cord's dimensions and administered topically, cell side down. The material will be stitched to the PMSC-ECM product. The fetal skin will thereafter be closed in the usual way. Antibiotics will also be added along with a replacement of the amniotic fluid volume in the womb.

Outcome Measures of CuRe Trial

Primary Outcome Measures:

Safety of the placenta-derived mesenchymal stem cell (PMSC-ECM) Product [Time Frame: Assessed at birth]

This will be evaluated to determine whether or not there is a cerebrospinal fluid leak, an infection at the MMC repair site, failure of the MMC repair site to heal, and development of any unexpected growths

or tumour formation. These outcomes will be evaluated by a physical examination, brain and spinal MRI, and brain and spinal ultrasonography after delivery.

Secondary Outcome Measures:

Efficacy of the PMSC-ECM Product [Time Frame: 30 months.]

This is mainly assessed by observing improvement in motor function exceeding two levels beyond what would be expected based on the anatomical level of the defect, along with evaluation of the patient's capacity for independent walking.Anorectal manometry and caregiver questionnaires on bowel habits will be used to evaluate bowel function. The evaluation of urologic function will be conducted through the use of video urodynamics, renal and bladder ultrasounds, and caregiver questionnaires to screen for hydronephrosis and abnormalities of the bladder

Conclusion

With the advancement in the world of medical science, the treatment of MMC is not a far-fetched idea. Comparative studies have revealed that in-utero intervention with placental mesenchymal stem cells is more successful than one done postnatally and has shown promising results in clinical trials for fetal surgery. However, prenatal surgery has its limitations such as neonatal bradycardia and respiratory distress syndrome. In comparison with other types of stem cells, placental mesenchymal stem cell therapy has shown maximum coverage when used during fetal surgery. After adequate experimentation with animal models, the placental mesenchymal stem cell is now being used in clinical trials with human subjects where the surgeon surgically sutures the biocompatible scaffold at the defective site. The trial is reported to be finished by early 2030. The current data proves the intervention is a positive modality. This intervention thus can bring a great deal of satisfaction to the scientific community and the lives of the patients affected by MMC.

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