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Letter to Editor

Correcting Pathological Mutations Prenatally in the Fetus on the Genetic Level

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Fetal gene therapy in utero represents an innovative approach to early treatment of hereditary diseases by intervening in the early stages of fetal development. The goal of this method is to prevent irreversible organ damage and significantly improve the life prospects of the unborn child. Despite its potential, the clinical application has been hindered by various factors, the need for highly invasive procedures, technical and safety challenges, and the lack of suitable animal models for research. Considering monogenic pediatric diseases like Pompe disease or mucopolysaccharidoses, it is an unmet need to develop prenatal fetal gene therapy approaches to treat fetal life from early genetic damage in pregnancy. This manuscript focus on prenatal gene therapy options to date and future perspectives in prenatal application in fetal development. The term in-utero gene therapy, also known as fetal gene therapy or prenatal gene therapy, refers to the idea of applying somatic gene therapies prenatally to the embryo to prevent genetically inherited diseases. One concept was developed by the physician and human geneticist Charles Coutelle [1,2]. According to him, intrauterine gene transfer has certain advantages over postnatal treatment. For example, it is believed that the embryo or fetus may better uptake the recombinant DNA than a born child, potentially leading to a lifelong production of the therapeutic gene product. It is also assumed that this treatment method results in significantly lower immune reactions against the vector and gene product. On the other hand, such a procedure carries certain risks, such as the risk of infections, triggering premature labor, and miscarriages. Additionally, unwanted germline influence cannot be definitively ruled out. Thus, not only risks for the carrying parent and the fetus itself are conceivable, but also for potential future generations. Establishing such a treatment method also requires research on human embryos. There is controversy over the conditions under which it would be justifiable to make embryos the subjects of such experiments. So far, this therapeutic approach has only been researched in animal models. Due to urgency, it is necessary to develop prenatal gene therapy options especially in rare genetic diseases, where a monogenetic cause was ruled out. For the future it could help in many different pediatric diseases, where the genetic defect is well known and a possible prenatal one-time gene approach is thinkable. Fetal gene therapy is the experimental concept of treating genetically inherited diseases prenatally by applying gene therapies to the fetus. The goal is to preventively treat severe, early-onset genetic diseases that would otherwise lead to significant limitations or death. Although still in the experimental stage, it is considered a promising method for treating genetic disorders developed based on an understanding of genetics and prenatal developmental stages. It is a concept for applying somatic gene therapies before birth. Preventing genetically inherited diseases that could lead to significant limitations after birth or even death is the major goal. The principle is to involve correcting gene defects to prevent the onset of diseases, especially in severe and early-onset genetic diseases. Fetal gene therapy is currently in a purely experimental stage. The first step would likely be genome editing of somatic cells to achieve non-inheritable changes for therapeutic purposes. The prevention of genetic diseases differs from germline therapy, which would cause an inheritable change and is prohibited in Germany. The method carries risks that need to be carefully weighed. The ethical evaluation is complex as it involves

intervention in a developing organism. The precise administration of gene therapy to the fetus and controlling its effects in developing tissue pose technical challenges. The therapy has a potential to prevent severe genetic diseases that would otherwise have lifelong consequences. It enables an improvement in quality of life by treating diseases at the earliest possible stage.

The present forms of fetal gene therapy are direct-in utero-gene therapy, in utero transplantation of gene-corrected cells, and maternal gene therapy. These approaches aim to correct genetic disorders before birth using techniques like gene addition or editing, with delivery methods varying from direct injection to using viral vectors. Direct-in-utero gene therapy involves the direct delivery of a corrective gene into fetal cells to treat a specific organ or tissue. The delivery methods are viral vectors like using modified viruses like lentiviruses or Adeno-Associated Viruses (AAV) to carry the gene into cells. Non-viral methods include naked DNA injection, electroporation, or ultrasound-mediated transfection. Targeted delivery is administering the gene directly into specific organs or by other routes such as intra-cardiac or intra-muscular, depending on the target site. The method of in utero transplantation of gene-corrected fetal stem cells involves genetically modifying the fetus's own stem cells to correct the genetic defect and then transplanting them back into the fetus. The process is performed by Hematopoietic Stem Cells (HSCs) as a key target, as they can be reprogrammed to favor the production of a protective protein after birth. This method has been used in animal models and some human fetuses, though clinical success has been limited by challenges with donor cell engraftment. The maternal gene therapy involves treating the mother to prevent the passage of a genetic disease to her child. The mechanism involves administering gene-altering treatments to the mother to correct a genetic deficiency that would otherwise be passed on to the fetus. General techniques are on the one hand gene addition by correction of a functional gene by adding to the cells. On the other hand, gene editing methods correct a mutation directly within the gene itself using tools like CRISPR-Cas9.

Pitfalls of fetal gene therapy include technical challenges, risks from the invasive procedures, potential for unintended consequences in fetal development, and significant ethical concerns about germline editing and consent. Specific dangers involve immune reactions, off-target effects, long-term side effects, and potential for complications like infection or preterm labor for the mother, and risks like cancer or fetal demise for the fetus. Technical and procedural risks include invasive procedures, vector limitations, delivery and control, unexpected gene expression, immune responses, developmental impacts, germline modifications, lack of consent and equity.

a) Invasive Procedures: Delivering the therapy requires invasive methods like injections, which carry risks of infection, bleeding, and preterm labor for the mother, and fetal demise for the fetus.

b) Vector Limitations: Current viral vectors may trigger adverse immune responses or have the potential for insertional mutagenesis. Non-viral vectors often have lower efficiency.

c) Delivery and Control: Precisely targeting the correct cells in a developing fetus is technically complex and challenging. The therapy may be difficult to control, leading to unpredictable outcomes.

d) Unexpected Gene Expression: The inserted gene could be expressed at the wrong time (untimely expression) or in the wrong place (ectopic expression), leading to unforeseen effects on fetal development.

e) Immune Responses: The fetus could have a negative immune reaction to the vector or the therapeutic protein.

f) Developmental Impacts: The therapy might have unknown short-term or long-term consequences that are difficult to predict, especially since the fetus has a developing immune system.

g) Oncogenesis: Rapidly dividing fetal cells may be more vulnerable to certain genetic alterations that could lead to cancer.

h) Lack of Consent: The fetus cannot consent to the procedure.

i) Germline Modification: Interventions that alter the germline can have permanent, heritable effects on future generations, raising concerns about unintended consequences.

j) Equity: The potential for high costs could lead to unequal access to the therapy.

Fetal gene therapy, also known as intrauterine or prenatal gene therapy, is still an experimental field that aims to preventively treat severe congenital genetic diseases before birth [3-7]. The methods focus on transferring genetic material, often using viral vectors into the fetus to correct the genetic predisposition of the disease [8-11]. Possible forms of fetal gene therapy are the use of viral vectors. Certain viruses are modified to be able to insert their genetic material into the human DNA of the fetus. Another method are liposomes that are artificial vesicles that transport the therapeutic genetic material and can insert it into the cells of the fetus. Chemical modification is a chemical method that could be used to facilitate the transfer of the therapeutic gene into the cells. Transplantation therapy uses modified cells like stem cells are transferred to the fetus to correct genetic defects. Prenatal exome sequencing analysis in fetuses with intrauterine structural developmental deformities was performed recently [12]. The goal is to prevent severe, early-onset genetic diseases by early treatment interventions like Pompe disease in early stages [13,14]. Treatment during the early developmental phase aims to significantly improve postnatal quality of life by correcting gene defects prenatally as

early as possible after prenatal diagnosis [15].

Conclusion

Intrauterine gene therapy is currently still largely in the experimental stage. It exclusively targets somatic gene therapy, where only the patient's body cells are corrected. Germ line gene therapy, alteration of the germ line, is legally prohibited in Germany to date. The future research will show which fetal gene therapy will be introduced in serious genetic diseases in childhood. But it will be the future of treating children as early as possible.

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Conflict of Interest

None.

References

1. Coutelle C (2005) Prenatal Gene Therapy: Scientific Foundations and Ethical Aspects of Prenatal Somatic Gene Therapy for Genetically Inherited Diseases. (Berlin Medical Ethics Papers: 55. Contributions to ethical and legal issues in medicine). Humanitas Verlag.
2. Coutelle C (2011) Intrauterine Gene Therapy: A Concept for Prenatal Prevention of Genetically Inherited Diseases. In B. Fehse & S. Domasch (Eds.), Gene Therapy in Germany: An Interdisciplinary Inventory PP: 127-150.
3. Barrachina L, Ivanovska A, Eslami Arshaghi T, O Brien A, Cequier A, et al. (2025) Generation of equine induced pluripotent stem cells from cells of embryonic, perinatal and adult tissues. Stem Cell Res Ther 16(1): 547.
4. Samoilova EM, Kalsin VA, Kushnir NM, Chistyakov DA, Troitskiy AV, et al. (2018) Adult Neural Stem Cells: Basic Research and Production Strategies for Neurorestorative Therapy. Stem Cells Int 2018: 4835491.
5. Miskinyte G, Devaraju K, Gronning Hansen M, Monni E, Tornero D, et al. (2017) Direct conversion of human fibroblasts to functional excitatory cortical neurons integrating into human neural networks. Stem Cell Res Ther 8(1): 207.
6. Rahim AA, Kurian MA, Zhou H, Ferguson R, Tabrizi SJ, et al. (2025) Genetic therapies for neurological diseases. Pharmacol Rev 78(1): 100093.
7. Gough G, Schaefer GO, Lim KMX, Choolani M, Mattar CNZ (2025) The future of clinical studies of in utero therapy for genetic diseases. Best Pract Res Clin Obstet Gynaecol 103: 102678
8. Martinez Garcia A, Tirado Aguilar OA, Acevedo Gallegos S, Gallardo Gaona JM, Velazquez Torres B, et al. (2025) Fetal cardiac rhabdomyomas susceptible to prenatal treatment with mTOR inhibitors: literature review and proposal of a prenatal management algorithm. Front Med (Lausanne) 12: 1711774.
9. Kao YT, Fan HC, Ro Lin Chang G, Chen JK, Yen CC, et al. (2025) Transformative approaches in hemophilia management: from traditional therapies to prenatal stem cell treatment. Front Bioeng Biotechnol 13: 1684096.
10. Martínez Sánchez N, Herrero B, Mansilla E, Prior de Castro C, De la Calle M, et al. (2025) Intrauterine Treatment in Two Fetuses Affected by Cystic Fibrosis: To Whom and Since When? Report of Cases. Fetal Diagn Ther: 1-9.
11. Türkçapar AF, Büken NÖ (2025) An ethical issue in the prenatal and postnatal management of trisomy 18: a survey of obstetricians. Ann Med 57(1): 2594283.
12. Jiang Y, Li H, Zhu X, Xu L, Chang Y, et al. (2025) Prenatal Exome Sequencing Analysis in Fetuses With Structural Anomalies: A Multicenter Prospective Cohort Study with Practical Implications. Prenat Diagn 46(1): 46-55.
13. Li C, Desai AK, Gupta P, Dempsey K, Bhambhani V, et al. (2021) Transforming the clinical outcome in CRIM negative infantile Pompe disease identified via newborn screening: the benefits of early treatment with enzyme replacement therapy and immune tolerance induction. Genet Med 23(5): 845 855.
14. Tsai AC, Hung YW, Harding C, Koeller DM, Wang J, et al. (2017) Next generation deep sequencing corrects diagnostic pitfalls of traditional molecular approach in a patient with prenatal onset of Pompe disease. Am J Med Genet A 173(9): 2500 2504.
15. Baran V, Čikoš Š, Fabian D (2025) The Consequences of DNA Damage in the Early Embryo Are Important for Practical Procedures in Assisted Reproduction. Int J Mol Sci (20): 10031.