Prenatal Interventions for the Treatment of Congenital Disorders

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12.1 Introduction

Regenerative medicine definition includes the use of diverse approaches to repair, replace or restore the functional loss of cells, tissues, or organs due to any etiology (Greenwood et al. 2006). Treating diseases as early as possible by correcting the defective tissues or replacing the defective cells is the primary concept behind regenerative medicine. The intent of treating the diseases before the onset of irreversible damage to the body has been the reason for the early intervention at the fetal stage. Moreover, the development of early diagnostic methodologies—imaging and molecular diagnosis—has provided us the opportunity to detect the disease-causing events early and consequently, intervene promptly to ameliorate the diseases.

There has been significant development in the field of in utero treatment approaches. On PubMed search, 29,665 search results appear for this systematic search (Table 12.1 and Fig. 12.1). About 70% of these articles have been published in this century (since 2000). With the development of gene replacement and gene editing technologies (targeted nucleases, base editors), the potential ability to correct severe and debilitating diseases are better than any time in the past.

Certain characteristics inherent to the fetus make it an ideal candidate for early intervention and modern advanced therapeutic strategies, for example, gene therapy and gene editing. Small size, less developed biological barriers (e.g., blood–brain barrier), accessible progenitor, and stem cells and immature immune response are some of the properties of the fetus which we can utilize for treating fatal genetic disorders (Flake 2003).

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N. Chakravorty, P. C. Shukla (eds.), *Regenerative Medicine*,
https://doi.org/10.1007/978-981-19-6008-6_12

Table 12.1 PubMed search results for in utero transplantation, gene therapy, and gene editing

Aim of search	Search term	Website	No. of search results
Identify literature of in utero transplantation, gene therapy and gene editing	(((transplantation) OR (gene therapy)) OR (gene editing)) AND ((fetal) OR ("in utero"))	PubMed Search formatted link: https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28transplantation%29+OR+%28gene+therapy%29%29+OR+%28gene+editing%29%29+AND+%28%28fetal%29+OR+%28%22in+utero%22%29%29&ac=no&sort=relevance	29,665 (Accessed on March 13, 2022)

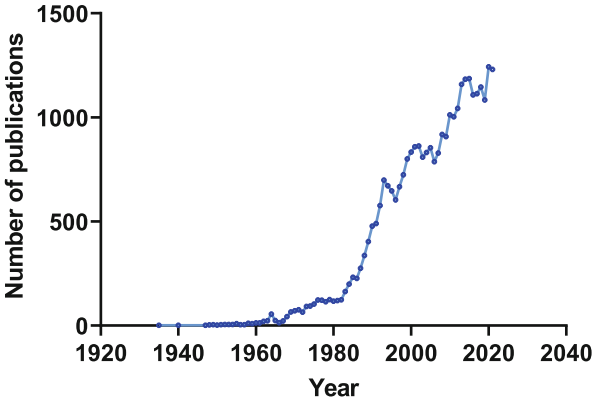

Fig. 12.1 Number of publications between 1935 and 2021 referring to fetal gene therapy and transplantation (PubMed search in Table 12.1)

The small size of the fetus allows us to maximize the dose per unit weight of the recipient and also provides a practical advantage in terms of the pharmaceutical dose we can deliver. For example, a fetus weighs 600 g compared to a 60 kg adult. So, less dose is needed to treat a fetus than an adult human, especially for advanced biological therapies, such as gene and cell therapy, where mass manufacturing is challenging. With the same amount of biological therapeutic product, we can treat more patients. Along similar lines, in a fetus, progenitor and stem cells are more prevalent and if we can correct these cells with advanced therapeutics, we can treat the diseases for the lifetime of the patient. Moreover, immunological and physical barriers are not well-developed in the fetus, which can allow us to deliver therapeutics early and help protect the patient when it comes out from the protective environment of the mother's womb.

The aim of this chapter is to summarize the preclinical research for in utero approaches (prenatal surgery, cell therapy, and gene therapy) for the treatment of genetic diseases.

12.2 Technological Advances in Early Diagnosis

Cutting-edge diagnostic, minimally invasive surgical approaches, and research methodologies reveal the mechanisms and etiologies of the diseases. Barcoded cells tracking helps in defining nesting locations of cells within the fetus (Wang et al. 2021a). Tracing developing fetal cells and identifying the trajectory of cells after transplantation are significant for the design of rational therapeutics. Barcoding the cells can be one such approach, as next-generation sequencing approaches have raised the sensitivity and specificity of detecting the minuscule amounts of nucleic acids (Wang et al. 2021b). Progress in predictive technology for the quality control of isolation of specific cell types opens prospects for future clinical applications (Zia et al. 2021). Several surgical and minimally invasive methods (e.g., fetoscopy) are already being used in the fetus to overcome severe anatomic and inflammatory anomalies, such as heart syndromes, twin-to-twin transfusion syndrome, myelomeningocele, and sacrococcygeal teratoma (Lin et al. 2021).

Early diagnostic methodologies such as non-invasive prenatal detection of disease-causing mutations in maternal plasma using digital droplet Polymerase Chain Reaction (PCR) (D'Aversa et al. 2022), next-generation sequencing, prenatal rapid exome sequencing (Mellis et al. 2022; Wei et al. 2022), copy-number variation detection (Cai et al. 2021), DNA methylation studies (reference-free and reference-based cell type estimation) (Dieckmann et al. 2022), non-invasive prenatal fetal blood group testing and coelocentesis will help in early detection of severe and incurable disorders (Clausen et al. 2022; Giambona et al. 2022; Wu et al. 2022). Couples (one or both) harboring chimeric heterozygous mutations may specifically be benefitted from early preimplantation genetic testing. In the study by Li et al. (2022a), the authors screened the embryos of a couple with heterozygous pathogenic mutation for osteogenesis imperfecta and then, implanted the wild-type embryo. Certain syndromes, such as Aicardi syndrome lack genetic tests to confirm the diagnosis of the disease, the development of early diagnostic methodologies, and mechanistic understanding may guide novel treatment strategies (Pomar et al. 2022). An increase in accessibility of modern fetal diagnostic and therapeutic approaches will allow for expanding the treatments to more patients in the future (Poojari et al. 2022).

12.3 Prenatal Pharmacotherapy

Fetal alcohol spectrum disorders (FASD) are a common cause of physical, cognitive, and behavioral abnormalities. A study into the mechanisms of this is divulging that early interventions based on the principles of central nervous system development and regeneration can ameliorate the damage (Gomez and Abdul-Rahman 2021). Administration of choline prenatally has shown to reduce the effects of prenatal alcohol exposure and leads to improved cognitive and behavioral outcomes (Wozniak et al. 2020).

For prenatally detected cardiac rhabdomyomas, transplacental sirolimus administration has been explored as a safe therapeutic option. However, there is a risk of sirolimus-associated growth restriction (Wozniak et al. 2020).

12.4 Prenatal Surgery

In utero surgery is commonly performed for photocoagulation of placental anastomosis in twin-twin transfusion syndrome to allow for equal sharing of blood between the twins (Codsi and Audibert 2019). Additionally, fetal surgery can be a potential option for the diseases like severe congenital diaphragmatic hernia with ineffective postnatal treatments and potential preclinical evidence of benefit by early surgical intervention. For example, it has been advocated that prenatal myelomeningocele repair in the carefully selected patient can have improved functional outcomes (Adzick et al. 2011; Peranteau and Adzick 2016). Despite vigilant patient selection and many parents opting for prenatal surgical intervention, a small group of parents chooses to terminate of pregnancy because of the risk of unexpected outcomes (Crombag et al. 2021). As more fetal therapy centers are conducting additional studies to catalog beneficial outcomes and the risk of complications, the results will support the decision process of stakeholders, especially parents (da Rocha et al. 2021; Lillegard et al. 2022; Moehrlen et al. 2021; Vonzun et al. 2021). Improved surgical approaches, for example, fetoscopic repair can reduce the risks associated with open repair (Cortes et al. 2021). However, premature delivery might be a risk for such interventions (Diehl et al. 2021).

Prenatal fetoscopic surgeries can have improved outcomes in congenital diaphragmatic hernia, fetal lower urinary tract obstruction, and ultrasound-guided fetal aortic valvuloplasty for hypoplastic left heart syndrome (Codsi and Audibert 2019). Moreover, in fetal lower umbilical tract obstruction, prenatal cystoscopy and fetal vesicoamniotic shunt did not show a difference in perinatal survival. The complication of urological fistula was found in 10% of patients, who underwent laser ablation. Technological advances, which can help direct the laser energy accurately in all fetal-placental positions, may reduce fistula-related complications (Vinit et al. 2020). Balanced, paired use of drugs, and surgery can be therapeutically synergistic; for example, the use of sildenafil and fetal tracheal occlusion has preclinically been shown to be beneficial in congenital diaphragmatic hernia (Russo et al. 2022).

In addition, knowledge gained from preclinical research in large animal models can help in improved outcomes of these novel surgical procedures (Coons et al. 2021).

12.5 Prenatal Cell Therapy

Prenatal mesenchymal, stromal, and epithelial stem cells transplantation is a valuable methodology for treating congenital disorders. Recently intraamniotic injection of amniotic mesenchymal stem cells can bring partial closure of spina bifida and improve functional outcomes (Kunpalin et al. 2021; Shieh et al. 2019).

Human amnion-derived epithelial cells (hAEC) possess stem cell-like properties and are capable to be differentiated into different cell types. In vitro, these cells have been differentiated into different cell types—hepatocyte-like cells, insulin-producing cells, islet-like cells, corneal epithelial-like cells, neural cells, osteogenic cells, epidermal cells, Schwann-like cells, and cardiomyocyte-like cells (Zhang and Lai 2020).

Alpha thalassemia major is one of the common monogenic disorders. Early diagnosis by percutaneous umbilical cord blood sampling, followed by in utero blood transfusion can produce favorable outcomes (MacKenzie et al. 2021; Hui et al. 2022; Horvei et al. 2021; Demirci et al. 2021). Postnatally, the patients can be managed with multiple transfusions or stem cell transplantation. Moreover, preclinical studies have shown successful transplantation of prenatal hematopoietic stem cells (Peranteau et al. 2002).

Fetoplacental extracellular vesicles (fEV) have been found to downregulate innate and adaptive immunity. In utero exposure to allogenic exosomes reduced the lymphocytic reaction to the allogenic antigens, however, it did not result in the tolerance to allogenic graft (Chen 2021a). In another study, transamniotic stem cell therapy using mesenchymal stem cells has been shown to reverse some of the effects of intrauterine growth retardation (IUGR) in a rat model (Labuz et al. 2022). Discoveries into the behavior of fetal macrophages can help in diving into novel treatment approaches. For example, fetal $CD116^{+}CD64^{-}$ macrophage precursors thrive better than the adult counterparts in perinatal lung alveoli. Fetal mesenchymal stromal cell extracellular vesicle can be beneficial in preventing preeclampsia-associated lung injury and ventilation-associated lung injury (Taglauer et al. 2022; Horie et al. 2021).

In utero mesenchymal stem cell therapy is also being investigated as a therapeutic option to prevent spontaneous abortions, hypothetically benefitting by inhibition of excessive complement activation and promoting the balance of angiogenic factors (Shahgaldi et al. 2022).

12.6 Prenatal Gene Therapy and Gene Editing

Gene therapy and gene editing (e.g., CRISPR-Cas9 system) approaches involve the administration of genetic material to modify the expression of genes and thus treat the diseased cells and tissues. Such molecules can be delivered prenatally by diverse routes of administration—vitelline vein, intraamniotic (Alapati et al. 2019), and intracerebral route (MacKenzie 2018).

CRISPR/Cas9 nucleases have shown to be therapeutically beneficial in diseases, for example, type 1 tyrosinemia and Surfactant protein C (SFTPC) deficiency. Moreover, recently base editors in the fetus have shown therapeutic benefits (Singh et al. 2021). Prime editing can be beneficial to treat those mutations which are not amenable to CRISPR-Cas9 nucleases or base editors (Anzalone et al. 2019).

Prenatal gene therapy and gene editing approaches can be beneficial in several genetic and metabolic diseases: sickle cell disease and thalassemia (Li et al. 2022b), spinal muscular atrophy (Rashnonejad et al. 2019), type 1 tyrosinemia (Singh et al. 2021; Rossidis et al. 2018), mucopolysaccharidoses (Bose et al. 2021), and surfactant protein C deficiency (Alapati et al. 2019). Transamniotic fetal immunotherapy can also be beneficial for some diseases (Whitlock et al. 2022).

12.7 Future Direction and Implications

The use of viral vectors for gene therapy and gene editing has been a concern among caregivers and patients. However, alternative delivery strategies such as lipid and synthetic polymer nanoparticles for the delivery of gene therapy and gene editing molecules have helped in removing some of the viral vector side effects, such as viral genome integration events (Ricciardi et al. 2018). The development of targeted fetal and tissue specific promoters to increase the specificity of gene expression, especially for gene editors, can also help in alleviating viral vectors associated adverse events (Singh et al. 2018).

Arguably, it has been considered that exposure of the fetus to foreign antigens can induce tolerability; however, the response of the fetus can vary with the type of antigenic exposure, and consequently, the results can be immunogenic or tolerogenic (Chen 2021b; Mold and McCune 2012). Therefore, careful preclinical investigation for the safety of the therapeutic molecules or cells should be the primary aspect of evaluation. Some large animal gene therapy with Adeno-associated viral vector (AAV) studies have observed an increase in the incidence of premature labor, compared to saline control injection. However, it is still unclear whether such premature labor is a result of specific viral vector formulations, contaminants, or species-specific response, since, other in utero studies in large animal models such as sheep, rhesus has been successful (Finkel and Lorson 2022). Systemic infusion of human amniotic epithelial cells can carry a risk of embolism, so further development of methodologies for safe transfusion (e.g., intraportal infusion) may ameliorate this risk (Tanaka et al. 2022).

High-throughput and high-resolution profiling of stem and progenitor cells by technological advances can increase the probability of divulging mechanisms of diseases and effects of gene therapy approaches (Vanuytsel et al. 2022). The role of immune checkpoint modulators (PD-1, Tim-3, VISTA) has been identified in determining the pregnancy outcome (Zhao et al. 2022). This new knowledge will help in unraveling the side effects associated with prenatal approaches and thus control the adverse outcomes of the diseases. Furthermore, awareness among parents and genetic counselors about the safety and efficacy of fetal treatments can increase

the acceptance of new fetal therapies (Scott et al. 2022). Interdisciplinary discoveries, targeted development of devices for targeted surgical and radiation delivery, robotics for precise surgical intervention, and understanding of biology, gene delivery and therapeutic vectors will pave way for prenatal therapy of several diseases, which are currently untreatable or have limited treatments. Additionally, interdisciplinarity should not only be applied in the context of medical technologies; however, considerations regarding the societal and ethical implications, along with maternal-fetal health, should be paramount (Brown and Koenig 2021).

References

Adzick NS, Thom EA, Spong CY, Brock JW, Burrows PK, Johnson MP, Howell LJ, Farrell JA, Dabrowiak ME, Sutton LN, Gupta N, Tulipan NB, D'Alton ME, Farmer DL (2011) A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med 364: 993–1004

Alapati D, Zacharias WJ, Hartman HA, Rossidis AC, Stratigis JD, Ahn NJ, Coons B, Zhou S, Li H, Singh K, Katzen J, Tomer Y, Chadwick AC, Musunuru K, Beers MF, Morrisey EE, Peranteau WH (2019) In utero gene editing for monogenic lung disease. Sci Transl Med 11. https://doi.org/10.1126/scitranslmed.aav8375

Anzalone AV, Randolph PB, Davis JR, Sousa AA, Koblan LW, Levy JM, Chen PJ, Wilson C, Newby GA, Raguram A, Liu DR (2019) Search-and-replace genome editing without double-strand breaks or donor DNA. Nature 576:149–157

Bose SK, White BM, Kashyap MV, Dave A, De Bie FR, Li H, Singh K, Menon P, Wang T, Teerdhala S, Swaminathan V, Hartman HA, Jayachandran S, Chandrasekaran P, Musunuru K, Jain R, Frank DB, Zoltick P, Peranteau WH (2021) In utero adenine base editing corrects multi-organ pathology in a lethal lysosomal storage disease. Nat Commun 12:4291

Brown JEH, Koenig BA (2021) Ethical, legal, and social implications of fetal gene therapy. Clin Obstet Gynecol 64:933–940

Cai M, Fu X, Xu L, Lin N, Huang H (2021) renatal diagnosis of 17p11.2 copy number abnormalities associated with Smith–Magenis and Potocki–Lupski syndromes in fetuses. Front Genet 12. https://www.frontiersin.org/article/10.3389/fgene.2021.779237

Chen J-C (2021a) Immunological consequences of in utero exposure to foreign antigens. Front Immunol 12:638435

Chen JC (2021b) Immunological consequences of in utero exposure to foreign antigens. Front Immunol 12:1227

Clausen FB, Hellberg Å, Bein G, Bugert P, Schwartz D, Drnovsek TD, Finning K, Guz K, Haimila K, Henny C, O'Brien H, Orzinska A, Sørensen K, Thorlacius S, Wikman A, Denomme GA, Flegel WA, Gassner C, de Haas M, Hyland C, Ji Y, Lane WJ, Nogués N, Olsson ML, Peyrard T, van der Schoot CE, Weinstock C, Legler T (2022) Recommendation for validation and quality assurance of non-invasive prenatal testing for foetal blood groups and implications for IVD risk classification according to EU regulations. Vox Sang 117:157–165

Codsi E, Audibert F (2019) Fetal surgery: past, present, and future perspectives. J Obstet Gynaecol Can 41:S287–S289

Coons BE, Lawrence KM, Didier R, Sridharan A, Moon JK, Rossidis AC, Baumgarten HD, Kim AG, Mejaddam AY, Ozawa K, De Bie F, Davey M, Flake AW (2021) Fetoscopic insufflation modeled in the extrauterine environment for neonatal development (EXTEND): fetoscopic insufflation is safe for the fetus. J Pediatr Surg 56:170–179

Cortes MS, Chmait RH, Lapa DA, Belfort MA, Carreras E, Miller JL, Samaha RBB, Gonzalez GS, Gielchinsky Y, Yamamoto M, Persico N, Santorum M, Otaño L, Nicolaou E, Yinon Y, Faig-Leite F, Brandt R, Whitehead W, Maiz N, Baschat A, Kosinski P, Nieto-Sanjuanero A,

Chu J, Kershenovich A, Nicolaides KH (2021) Experience of 300 cases of prenatal fetoscopic open spina bifida repair: report of the International Fetoscopic Neural Tube Defect Repair Consortium. Am J Obstet Gynecol 225(678):e1–678.e11

Crombag N, Sacco A, Stocks B, De Vloo P, van der Merwe J, Gallagher K, David A, Marlow N, Deprest J (2021) 'We did everything we could'—a qualitative study exploring the acceptability of maternal-fetal surgery for spina bifida to parents. Prenat Diagn 41:910–921

D'Aversa E, Breveglieri G, Boutou E, Balassopoulou A, Voskaridou E, Pellegatti P, Guerra G, Scapoli C, Gambari R, Borgatti M (2022) Droplet digital PCR for non-invasive prenatal detection of fetal single-gene point mutations in maternal plasma. Int J Mol Sci 23:2819

da Rocha LSN, Bunduki V, de Amorim Filho AG, Cardeal DD, Matushita H, Fernandes HS, Nani FS, de Francisco RPV, de Carvalho MHB (2021) Open fetal myelomeningocele repair at a university hospital: surgery and pregnancy outcomes. Arch Gynecol Obstet 304:1443–1454

Demirci S, Leonard A, Essawi K, Tisdale JF (2021) CRISPR-Cas9 to induce fetal hemoglobin for the treatment of sickle cell disease. Mol Ther Methods Clin Dev 23:276–285

Dieckmann L, Cruceanu C, Lahti-Pulkkinen M, Lahti J, Kvist T, Laivuori H, Sammallahti S, Villa PM, Suomalainen-König S, Rancourt RC, Plagemann A, Henrich W, Eriksson JG, Kajantie E, Entringer S, Braun T, Räikkönen K, Binder EB, Czamara D (2022) Reliability of a novel approach for reference-based cell type estimation in human placental DNA methylation studies. Cell Mol Life Sci 79:115

Diehl D, Belke F, Kohl T, Axt-Fliedner R, Degenhardt J, Khaleeva A, Oehmke F, Faas D, Ehrhardt H, Kolodziej M, Uhl E, Windhorst AC, Neubauer BA (2021) Fully percutaneous fetoscopic repair of myelomeningocele: 30-month follow-up data. Ultrasound Obstet Gynecol 57:113–118

Finkel RS, Lorson CL (2022) Friend or Foe(tal): challenges in development of a large animal model for pre-clinical fetal gene therapy. Gene Ther 29(6):316–318. https://www.nature.com/articles/s41434-022-00327-4

Flake AW (2003) Surgery in the human fetus: the future. J Physiol 547:45–51

Giambona A, Vinciguerra M, Leto F, Cassarà F, Cucinella G, Cigna V, Orlandi E, Piccione M, Picciotto F, Maggio A (2022) Very early prenatal diagnosis of Cockayne's syndrome by coelocentesis. J Obstet Gynaecol 42(5):1524–1531

Gomez DA, Abdul-Rahman OA (2021) Fetal alcohol spectrum disorders: current state of diagnosis and treatment. Curr Opin Pediatr 33:570–575

Greenwood HL, Singer PA, Downey GP, Martin DK, Thorsteinsdóttir H, Daar AS (2006) Regenerative medicine and the developing world. PLoS Med 3:e381

Horie S, Gonzalez H, Brady J, Devaney J, Scully M, O'Toole D, Laffey JG (2021) Fresh and cryopreserved human umbilical-cord-derived mesenchymal stromal cells attenuate injury and enhance resolution and repair following ventilation-induced lung injury. Int J Mol Sci 22:12842

Horvei P, MacKenzie T, Kharbanda S (2021) Advances in the management of α-thalassemia major: reasons to be optimistic. Hematology 2021:592–599

Hui PW, Pang P, Tang MHY (2022) 20 years review of antenatal diagnosis of haemoglobin Bart's disease and treatment with intrauterine transfusion. Prenat Diagn 42(9):1155–1161. https://doi.org/10.1002/pd.6125

Kunpalin Y, Subramaniam S, Perin S, Gerli MFM, Bosteels J, Ourselin S, Deprest J, De Coppi P, David AL (2021) Preclinical stem cell therapy in fetuses with myelomeningocele: a systematic review and meta-analysis. Prenat Diagn 41:283–300

Labuz DF, Whitlock AE, Kycia I, Zurakowski D, Fauza DO (2022) Intrauterine Growth Restriction (IUGR) as a potential target for transamniotic stem cell therapy. J Pediatr Surg 57(6):999–1003. S0022-3468(22)00141–5

Li C, Hou R, Liu C, Li H, Li-Ling J, Lyu Y (2022a) [Identification of pathogenic variant and preimplantation genetic testing for a Chinese family affected with osteogenesis imperfecta]. Zhonghua Yi Xue Yi Chuan Xue Za Zhi 39:21–25

Li L et al (2022b) Genetic correction of concurrent α- and β-thalassemia patient-derived pluripotent stem cells by the CRISPR-Cas9 technology | EndNote Click. Stem Cell Res Ther 13:102.

https://click.endnote.com/viewer?doi=10.1186%2Fs13287-022-02768-5&token=WzI1NzA4MzIsIjEwLjExOD Y vc z E z M j g 3 L T A y M i 0 w M j c 2 O C 0 1 I l 0 . W j 2 jLY6HvwTBLkZZWuwVTsbQWkA

Lillegard JB, Eyerly-Webb SA, Watson DA, Bahtiyar MO, Bennett KA, Emery SP, Fisher A, Goldstein RB, Goodnight WH, Lim F-Y, McCullough LB, Moehrlen U, Moldenhauer JS, Moon-Grady AJ, Ruano R, Skupski DW, Treadwell MC, Tsao K, Wagner AJ, Zaretsky MV (2022) Placental location in maternal-fetal surgery for myelomeningocele. Fetal Diagn Ther 49(3):117–124. https://doi.org/10.1159/000521379

Lin T-Y, Wataganara T, Shaw SW (2021) From non-invasive to invasive fetal therapy: a comprehensive review and current update. Taiwan J Obstet Gynecol 60:595–601

MacKenzie TC (2018) Future AAVenues for in utero gene therapy. Cell Stem Cell 23:320–321

MacKenzie TC, Amid A, Angastiniotis M, Butler C, Gilbert S, Gonzalez J, Keller RL, Kharbanda S, Kirby-Allen M, Koenig BA, Kyono W, Lal A, Lianoglou BR, Norton ME, Ogasawara KK, Panchalee T, Rosner M, Schwab M, Thompson A, Waye JS, Vichinsky E (2021) Consensus statement for the perinatal management of patients with α thalassemia major. Blood Adv 5:5636–5639

Mellis R, Eberhardt R, Hamilton S, PAGE Consortium, McMullan D, Kilby M, Maher E, Hurles M, Giordano J, Aggarwal V, Goldstein D, Wapner R, Chitty L (2022) Fetal exome sequencing for isolated increased nuchal translucency: should we be doing it? BJOG Int J Obstet Gynaecol 129:52–61

Moehrlen U, Ochsenbein N, Vonzun L, Mazzone L, Horst M, Schauer S, Wille DA, Hagmann C, Kottke R, Grehten P, Casanova B, Strübing N, Moehrlen T, Tharakan S, Padden B, Bassler D, Zimmermann R, Meuli M (2021) Fetal surgery for spina bifida in Zurich: results from 150 cases. Pediatr Surg Int 37:311–316

Mold JE, McCune JM (2012) Mccune. In: Advances in immunology. Elsevier, pp 73–111

Peranteau WH, Adzick NS (2016) Prenatal surgery for myelomeningocele. Curr Opin Obstet Gynecol 28:111–118

Peranteau WH, Hayashi S, Hsieh M, Shaaban AF, Flake AW (2002) High-level allogeneic chimerism achieved by prenatal tolerance induction and postnatal nonmyeloablative bone marrow transplantation. Blood 100:2225–2234

Pomar L et al (2022) Prenatal diagnosis of Aicardi syndrome based on a suggestive imaging pattern: a multicenter case-series. Prenat Diagn 42(4):484–494. Wiley Online Library. https://obgyn.onlinelibrary.wiley.com/doi/10.1002/pd.6085

Poojari VG, Paladugu S, Vasudeva A, Mundkur A, Pai MV, Kumar P (2022) We need to improve prenatal screening practices in primary obstetric care: a representative data from a fetal medicine unit in coastal Karnataka. J Obstet Gynaecol India 72:19–25

Rashnonejad A, Amini Chermahini G, Gündüz C, Onay H, Aykut A, Durmaz B, Baka M, Su Q, Gao G, Özkınay F (2019) Fetal gene therapy using a single injection of recombinant AAV9 rescued SMA phenotype in mice. Mol Ther 27:2123–2133

Ricciardi AS, Bahal R, Farrelly JS, Quijano E, Bianchi AH, Luks VL, Putman R, López-Giráldez F, Coşkun S, Song E, Liu Y, Hsieh W-C, Ly DH, Stitelman DH, Glazer PM, Saltzman WM (2018) In utero nanoparticle delivery for site-specific genome editing. Nat Commun 9:2481. https://doi.org/10.1038/s41467-018-04894-2

Rossidis AC, Stratigis JD, Chadwick AC, Hartman HA, Ahn NJ, Li H, Singh K, Coons BE, Li L, Lv W, Zoltick PW, Alapati D, Zacharias W, Jain R, Morrisey EE, Musunuru K, Peranteau WH (2018) In utero CRISPR-mediated therapeutic editing of metabolic genes. Nat Med 24:1513–1518

Russo FM, Da Cunha MGMCM, Jimenez J, Lesage F, Eastwood MP, Toelen J, Deprest J (2022) Complementary effect of maternal sildenafil and fetal tracheal occlusion improves lung development in the rabbit model of congenital diaphragmatic hernia. Ann Surg 275:e586–e595

Scott DA, Gofin Y, Berry AM, Adams AD (2022) Underlying genetic etiologies of congenital diaphragmatic hernia. Prenat Diagn 42(3):373–386. https://doi.org/10.1002/pd.6099

Shahgaldi S, Rezaei Kahmini F, Moazzeni SM (2022) Mesenchymal stem cell therapy attenuates complement C3 deposition and improves the delicate equilibrium between angiogenic and anti-angiogenic factors in abortion-prone mice. Mol Immunol 141:246–256

Shieh HF, Tracy SA, Hong CR, Chalphin AV, Ahmed A, Rohrer L, Zurakowski D, Fauza DO (2019) Transamniotic stem cell therapy (TRASCET) in a rabbit model of spina bifida. J Pediatr Surg 54:293–296

Singh K, Evens H, Nair N, Rincón MY, Sarcar S, Samara-Kuko E, Chuah MK, VandenDriessche T (2018) Efficient in vivo liver-directed gene editing using CRISPR/Cas9. Mol Ther 26:1241–1254

Singh K et al (2021) In utero lipid nanoparticle delivery of CRISPR technology to correct hereditary tyrosinemia type ASGCT annual meeting abstracts. Mol Ther 29:1–427

Taglauer ES et al (2022) Antenatal mesenchymal stromal cell extracellular vesicle therapy prevents preeclamptic lung injury in mice. Am J Respir Cell Mol Biol 66(1):86–95. https://www.atsjournals.org/doi/10.1165/rcmb.2021-0307OC

Tanaka M, Tokodai K, Sato M, Yamada S, Okita H, Ito T, Saito M, Hoshiai T, Miyagi S, Miki T, Unno M, Kamei T, Goto M (2022) Distribution of amniotic epithelial cells after intraportal infusion in a rat model. Transplant Proc 54(2):513–515. https://doi.org/10.1016/j.transproceed.2021.09.077

Vanuytsel K, Yeung AK, Dowrey TW, Murphy GJ, Belkina AC (2022) Comprehensive phenotyping of hematopoietic stem and progenitor cells in the human fetal liver. Cytometry A. https://doi.org/10.1002/cyto.a.24540

Vinit N, Gueneuc A, Bessières B, Dreux S, Heidet L, Salomon R, Lapillonne A, De Bernardis G, Salomon LJ, Stirnemann JJ, Blanc T, Ville Y (2020) Fetal cystoscopy and vesicoamniotic shunting in lower urinary tract obstruction: long-term outcome and current technical limitations. Fetal Diagn Ther 47:74–83

Vonzun L, Kahr M, Noll F, Mazzone L, Moehrlen U, Meuli M, Hüsler M, Krähenmann F, Zimmermann R, Ochsenbein-Kölble N (2021) Systematic classification of maternal and fetal intervention-related complications following open fetal myelomeningocele repair—results from a large prospective cohort. BJOG Int J Obstet Gynaecol 128:1184–1191

Wang M-Y, Zhou Y, Lai G-S, Huang Q, Cai W-Q, Han Z-W, Wang Y, Ma Z, Wang X-W, Xiang Y, Fang S-X, Peng X-C, Xin H-W (2021a) DNA barcode to trace the development and differentiation of cord blood stem cells (Review). Mol Med Rep 24:849

Wang M-Y, Zhou Y, Lai G-S, Huang Q, Cai W-Q, Han Z-W, Wang Y, Ma Z, Wang X-W, Xiang Y, Fang S-X, Peng X-C, Xin H-W (2021b) DNA barcode to trace the development and differentiation of cord blood stem cells (Review). Mol Med Rep 24:1–10

Wei X, Zhou X, Zhou J, Zou G, Yang Y, Zhou F, Xiong S, Chen J, Sun L (2022) The value of exome sequencing in thoracoamniotic shunt for severe pleural effusion with fetal hydrops: a retrospective clinical study. Fetal Diagn Ther. https://doi.org/10.1159/000521212

Whitlock AE, Labuz DF, Kycia I, Zurakowski D, Fauza DO (2022) Passive perinatal immunotherapy via transamniotic antibody delivery. J Pediatr Surg 57:52–55

Wozniak JR, Fink BA, Fuglestad AJ, Eckerle JK, Boys CJ, Sandness KE, Radke JP, Miller NC, Lindgren C, Brearley AM, Zeisel SH, Georgieff MK (2020) Four-year follow-up of a randomized controlled trial of choline for neurodevelopment in fetal alcohol spectrum disorder. J Neurodev Disord 12:9

Wu Q, Zheng L, Huang H, Lin H, Lin X, Xu L, Chen R, Lin D, Chen G (2022) Rapid and label-free prenatal detection of Down's syndrome using body fluid surface enhanced Raman spectroscopy. J Biomed Nanotechnol 18:243–250

Zhang Q, Lai D (2020) Application of human amniotic epithelial cells in regenerative medicine: a systematic review. Stem Cell Res Ther 11:439

Zhao S-J, Muyayalo KP, Luo J, Huang D, Mor G, Liao A-H (2022) Next generation of immune checkpoint molecules in maternal-fetal immunity. Immunol Rev 308(1):40–54. https://doi.org/10.1111/imr.13073

Zia S, Martini G, Pizzuti V, Maggio A, Simonazzi G, Reschiglian P, Bonsi L, Alviano F, Roda B, Zattoni A (2021) A new predictive technology for perinatal stem cell isolation suited for cell therapy approaches. Micromachines 12:782