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Maternal and fetal safety outcomes after in utero stem cell injection: A systematic review

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Abstract

Objective: To investigate the maternal and fetal safety of In utero stem cell transplantation (IUSCT).

Methods: Medline®, Embase and Cochrane library (1967–2023) search for publications reporting IUSCT in humans. Two reviewers independently screened abstracts and full-text papers.

Results: Sixty six transplantation procedures in 52 fetuses were performed for haemoglobinopathies ($n = 14$), red cell/bleeding disorders ($n = 4$), immunodeficiencies ($n = 15$), storage disorders ($n = 7$), osteogenesis imperfecta ($n = 2$) and healthy fetuses ($n = 10$). The average gestational age was 18.9 weeks; of procedures reporting the injection route, cells were delivered by intraperitoneal ($n = 37$), intravenous ($n = 19$), or intracardiac ($n = 4$) injection or a combination ($n = 3$); most fetuses received one injection ($n = 41$). Haematopoietic ($n = 40$) or mesenchymal ($n = 12$) stem cells were delivered. The cell dose was inconsistently reported (range 1.8–3.3 $\times$ 10^9 cells total ($n = 27$); 2.7–5.0 $\times$ 10^9/kg estimated fetal weight ($n = 17$)). The acute fetal procedural complication rate was 4.5% (3/66); the acute fetal mortality rate was 3.0% (2/66). Neonatal survival was 69.2% (36/52). Immediate maternal and pregnancy outcomes were reported in only 30.8% (16/52) and 44.2% (23/52) of cases respectively. Four fetal/pregnancy outcomes would also classify as $\geq$ Grade 2 maternal adverse events.

Conclusions: Short-, medium-, and long-term maternal and fetal adverse events should be reported in all IUSCT studies.

Key points

What is already known about this topic?

- Fetal therapy, such as fetal blood transfusion, is commonly used to treat fetal anemia with a good fetal safety profile. Certain genetic disorders such as Osteogenesis Imperfecta (OI) and α thalassaemia major are commonly diagnosed prenatally. These diseases may be

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amenable to treatment by In utero stem cell transplantation (IUSCT). Clinical trials will require an understanding of the safety of IUSCT for both mother and fetus.

What does this study add? (67 words)

- This systematic review found that the acute fetal complication rate of IUSCT was 4.5% per procedure. Fetal outcomes were commonly the focus of publications. Maternal adverse events and pregnancy outcomes have been poorly reported. As fetal therapeutic procedures must balance maternal and fetal risk/benefit, we recommend that studies of in utero cell transplantation report not only on efficacy but also maternal and fetal adverse events.

1 | INTRODUCTION

In utero stem cell transplantation with haematopoietic (HSC) or mesenchymal stem cells (MSC) may allow prenatal treatment of congenital diseases. The widespread availability of high-resolution fetal ultrasound imaging and advances in prenatal molecular diagnostic techniques means that such disorders are increasingly diagnosed early in gestation. In utero stem cell transplantation may enable treatment of life-threatening disorders before birth, ameliorate in utero damage and potentially provide curative treatment.[1]

The administration of stem cells to the fetus capitalises on the extensive fetal stem cell migration and expansion that occurs in utero.[2] Given the small size of the mid-trimester fetus, it also permits the administration of a higher cell dose per unit of recipient weight, which may improve engraftment. Compared with postnatal treatment, prenatal treatment offers the physiological advantage of the fetal circulation, which mainly bypasses the pulmonary vasculature, hence avoiding the sequestration of the injected stem cells in the lungs.[3] IUSCT also offers the potential to reconstitute an absent or damaged cell type without the need for myeloablation, or to induce prenatal tolerance to facilitate postnatal transplantation, utilizing fetal immunological naivety. Finally, prenatal therapy may offer a positive psychological benefit to parents, which should not be undervalued.[4]

The earliest report of IUSCT was in 1967 when a fetus with haemolytic disease due to Rh blood group alloimmunisation received fetal bone marrow HSC.[5] In 1988, the first successful report of IUSCT with HSC emerged, detailing a fetus with Bare Lymphocyte Syndrome who showed full reconstitution of the T cell compartment after umbilical vein injection of fetal liver derived HSC.[6] IUSCT with MSC was first successfully reported in 2004, for a fetus with OI.[7, 8] Clinical translation of IUSCT must not only present advantages over postnatal treatment but also safe for both the pregnant woman and the fetus. In utero stem cell transplantation is performed via an identical procedure to in utero blood transfusion, with the injection ideally administered into the intrahepatic umbilical vein under ultrasound image-guidance.[9] Whilst the immediate post procedural risks of IUSCT are likely to be similar to those of in utero blood transfusion,[9] little is known about complications during the remainder of the pregnancy, particularly maternal adverse events.

Two clinical trials of IUSCT are in progress. The first investigates a combined in utero injection of maternal bone marrow-derived HSC and blood transfusion for fetuses with α thalassaemia major (ClinicalTrials.gov Identifier: NCT02986698). The BOOSTB4 (Boost Brittle Bones Before Birth) trial studies the safety and efficacy of in utero and postnatal transplantation of first trimester human fetal liver-derived MSC for severe OI (ClinicalTrials.gov Identifier: NCT03706482). We undertook a systematic review of fetal and maternal safety of IUSCT providing comprehensive data to inform regulatory authorities, patients and healthcare professionals about IUSCT and to understand the timing of reported adverse events in order to develop optimal monitoring following IUSCT.

2 | OBJECTIVES

This systematic review investigated the fetal and maternal safety of IUSCT to support regulatory and ethical approval for clinical trials of IUSCT.

3 | METHODS

3.1 | Protocol and registration

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidance.[10] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42018110523), with the study title 'Maternal and fetal complications of in utero stem cell therapy'.

3.2 | Eligibility criteria

The condition being studied was (1) 'In utero injection of stem cells,' (2) participants were "Pregnant women and their fetuses" and (3) the intervention to be studied was 'In utero injection of haematopoietic or MSC into the fetal circulation'. All publications (randomised, cohort and case-controlled studies, case series, case reports, systematic reviews and narrative review articles) reporting the results of IUSCT in humans were eligible. No comparator groups were considered. No language or date restrictions were applied.

3.3 | Search strategy

A systematic search was conducted in Medline®, Embase and the Cochrane library databases using free text and Medical Subject Headings. Reference lists of relevant review articles were manually checked. Covidence (Veritas Health Innovation Ltd, Melbourne, Australia) was used to eliminate duplicate articles and manage study screening. The initial searches were performed electronically on 25/9/2018, and repeated on 24/6/2023. Search terms were:

- Title (prenatal OR fetus OR fetal OR "in utero" OR intrauterine)
- AND ("Stem cell")
- AND (Transplant*)

3.4 | Study selection

Two reviewers (RS and LWJ) reviewed titles and abstracts independently and excluded irrelevant studies. The same two reviewers independently performed full-text screening; disagreements were resolved by discussion. Studies were excluded at the full text screening stage if the full text was unavailable and the abstract contained insufficient information or if duplication had occurred. Studies involving only animals, postnatal stem cell administration, or stem-cell administration into the uterus outside of pregnancy were excluded. Studies were divided into original case publications and review articles. The same two reviewers analyzed the references of all review articles and identified relevant original publications referenced in these reviews. For inclusion in the final data set, publications had to contain details of the IUSCT along with at least one outcome measure. Only publications detailing original cases (or where published authors referred to their own unpublished information) were included (Table 1).

3.5 | Data extraction

Two reviewers (RS and LWJ) independently extracted data and entered it into a standardised Excel form. Disagreements were resolved by discussion. Characteristics noted included publication type, underlying fetal condition, type of stem cells administered, gestational age of fetus, route of administration, cell dose given and number of injections. To classify adverse events, we used definitions and grading 1–5 for maternal and fetal adverse events as per the Maternal and Fetal Adverse Event Terminology (MFAET) version 1.1 terminology, which is mapped to the Medical Dictionary of Regulatory Activities (MedDRA).[77, 78] The primary outcome measures were maternal or fetal mortality or morbidity possibly or probably related to the stem cell injection procedure. Where complications were reported, both reviewers assessed whether the adverse event was possibly or probably related to the IUSCT procedure or if it was unrelated. Unrelated adverse events were defined if they were related to a separate procedure from the IUSCT injection or due to an underlying fetal/maternal condition. To capture this information, outcomes documented included complications at the time of procedure, pregnancy and delivery details, long term fetal outcome and maternal complications. The acute fetal procedure complications and mortality rates are provided in relation to the number of needling procedures performed rather than the number of pregnancies in which IUSCT took place, as per best practise guidance.[9]

3.6 | Analysis strategy

A narrative synthesis was planned as it was anticipated that the publications identified would mainly consist of individual case reports detailing IUSCTs for a wide variety of conditions. Quality assessment of studies, assessment of heterogeneity and meta-analysis were not considered possible in these circumstances.

4 | RESULTS

4.1 | Study selection

The study selection process was carried out in two stages in order to identify all relevant original reports (Figure 1). During the primary search, both original reports and review articles were included. A secondary review of all references generated from the review articles then took place to identify any original reports not found by the primary search. The electronic literature search identified 618 studies published from 1967 to 24/06/2023. Following the study selection, 69 papers detailing 66 IUSCT procedures in 52 women were included in the final data set (Figure 1).

4.2 | Study characteristics

The 69 papers were independently read by both reviewers and all data were extracted. When cases were reported in a number of publications, all data were combined from the relevant publications to give the most robust data set. 52 cases were found, which contained sufficient information to analyze. Fourteen additional cases of IUSCT were identified in the search but were not included in the statistical data analysis as there was insufficient information to analyze (Supporting Information S1).

5 | DETAILS OF IUSCT CASES

There were 52 cases of IUSCT included, published between 1967 and 2020 (Table 1). These fetuses received a total of 66 IUSCT injections; most fetuses (n = 41) received a single injection, but eight fetuses received two injections each and three fetuses received three

TABLE 1 Summary table of the final data set after the selection procedure.

Reference	Also referenced in	Disease	Cell type	Cell source	Donor	Cell dose	Injection route	Gestational age	No of injections
Cowan and Golbus[11]	Diukman and Golbus[12], Golbus[13]	α thalassaemia major	HSC	Bone marrow	Maternal	6.3×10^8 cells total	IP	18	1
		Chediack Higashi	HSC	Bone marrow	Maternal	7.0×10^8 cells total	IP	19	1
		SCID	HSC	Bone marrow	Maternal	6.5×10^8 cells total	IV and IP	20	1
Davis[14]	N/A	Rh blood group alloimmunisation	HSC	Bone marrow	Unrelated	1 mL	IP (hysterotomy)	11	1
Flake et al.[15]	Zanjani et al.[16]	SCID	HSC	Bone marrow	Paternal	1.14×10^8 cells/kg, 1.48×10^7 cells total	IP	16	3
						8.9×10^6 cells/kg, 2.0×10^6 cells total	IP	17	
						6.2×10^6 cells/kg, 1.8×10^6 cells total	IP	18	
Flake and Zanjani[17]	N/A	CGD	HSC	Bone marrow	Paternal	N/S	N/S	15	1
		Hurler syndrome	HSC	Fetal liver	Unrelated	N/S	N/S	14	1
Götherström et al.[18]	Le Blanc et al[19], Le Blanc et al[8], Westgren et al[20], Westgren[21], Chan and Gotherstrom[22], Gotherstrom et al.[23]	OI	MSC	Fetal liver	Unrelated	3.0×10^7 cells/kg, 4.0×10^7 cells total	IV	31	1
		OI	MSC	Fetal liver	Unrelated	6.5×10^6 cells total	IV	32	1
Hayward et al.[24]	Eddleman[25]	α thalassaemia major	HSC	Bone marrow	Paternal	3.0×10^6 cells/kg	IP	13	3
						3.0×10^6 cells/kg	IV	19	
						3.0×10^6 cells/kg	IV	24	
Leung et al.[26]	Bambach et al[27], Blakemore et al[28]	Globoid cell leukodystrophy	HSC	Bone marrow	Paternal	5.0×10^9 cells/kg	IP	13	1
		Globoid cell leukodystrophy	HSC	Bone marrow	Paternal	5.0×10^8 cells/kg	IP	13	1
		Globoid cell leukodystrophy	HSC	Bone marrow	Paternal	5.0×10^8 cells/kg	IP	13	1
Linch et al.[29]	N/A	Rh blood group alloimmunisation	HSC	Bone marrow	Maternal	2.7×10^6 cells/kg	IV (fetoscopy)	17	1
Magnani et al.[30]	N/A	SCID	HSC	Bone marrow	Sibling	1.5×10^7 cells total	IV	25	1
McKenzie et al.[31]	Lianoglou[32]	α thalassaemia major	HSC	Bone marrow	Maternal	1×10^8 CD34+ cells/kg	IV	23	1
		α thalassaemia major	HSC	Bone marrow	Maternal	5×10^7 CD34+ cells/kg	IV	25	1
Muench et al.[33]	Harrison[34]	CGD	HSC	Bone marrow	Paternal	1.19×10^7 cells total	IP	14	1
Orlandi et al.[35]	N/A	β thalassaemia major	HSC	Fetal blood	Sibling	0.8 mL	IV	19	1

TABLE 1 (Continued)

Reference	Also referenced in	Disease	Cell type	Cell source	Donor	Cell dose	Injection route	Gestational age	No of injections
Pirovano et al.[36]	Pirovano et al[1], Porta et al[37], Porta et al[38], Bartoleme et al[39], Gil et al[40], Lanfranchi et al[41], Lanfranchi[42], Wengler et al[43], Ugazio et al[44]	SCID	HSC	Bone marrow	Paternal	1.4×10^7 cells total	IP	21	2
						4.0×10^6 cells total	IP	22	
		SCID	HSC	Bone marrow	Paternal	N/S	IP	21–25[c]	2
						N/S	IP	21–25[c]	
		SCID	HSC	Bone marrow	Paternal	1.6×10^7 cells/kg[b]	IP	21–25[c]	2
							IP	21–25[c]	
		SCID	HSC	Bone marrow	Paternal	2.0×10^7 cells/kg[b]	IP	21–25[c]	2
							IP	21–25[c]	
		Omenn syndrome	HSC	Adult blood	Maternal	4.0×10^7 cells/kg[b]	IP	22	2
							IP	23	
Renda and Maggio[45]	Renda et al[46], Renda et al[47]	β thalassaemia major	HSC	Adult blood	Paternal	4.0×10^7 cells/kg, 1.4×10^7 cells total	IV	20	1
		β thalassaemia major	HSC	Adult blood	Paternal	3.8×107 cells/kg, 1.7×107 cells total	IV	21	1
Sanna[48]	Monni et al[49]	β thalassaemia major	HSC	Bone marrow	Paternal	3.0×10^6 cells total[b]	IP	12	3
							IP	14	
							IP	16	
Slavin et al.[50]	N/A	β thalassaemia major	HSC	Bone marrow	Sibling	3.0×10^9 cells total	IV and IP	25	1
		Metachromatic leukodystrophy	HSC	Bone marrow	Paternal	3.3×10^9 cells total	IP	34	1
		Metachromatic leukodystrophy	HSC	Bone marrow	Paternal	3.0×10^9 cells total	IV and IP	23	1
Thilaganthan et al.[51]	N/A	Rh blood group alloimmunisation	HSC	Bone marrow	Maternal	2.3×10^7 cells total	IP	12	1

(Continues)

TABLE 1 (Continued)

Reference	Also referenced in	Disease	Cell type	Cell source	Donor	Cell dose	Injection route	Gestational age	No of injections
Touraine et al.[52]	Raudrant et al[53], Touraine[6], Touraine[54], Touraine[55, 56], Touraine[57, 58], Touraine[59], Touraine[60, 61], Touraine[62], Touraine[63], Touraine[64], Touraine[65], Touraine[66], Touraine[67, 68], Touraine[69], Touraine et al.[70], Touraine et al.[54], Touraine et al.[55] Touraine et al.[58], Touraine et al.[71], Touraine et al.[72], Touraine et al.[73], Touraine et al.[67]	β thalassaemia major	HSC	Fetal liver	Unrelated	3.0×10^8 cells total	IP	14[a]	1
		β thalassaemia major	HSC	Fetal liver	Unrelated	N/S	IV	19[a]	1
		Bare Lymphocyte Syndrome	HSC	Fetal liver/ thymic cells	Unrelated	1.6×10^7 cells total	IV	30[a]	1
		CGD	HSC	Fetal liver	Unrelated	N/S	IV	19[a]	2
						N/S	IV	23[a]	
		Hemophilia A	HSC	Fetal liver	Unrelated	N/S	N/S	15[a]	1
		Niemann Pick	HSC	Fetal liver	Unrelated	N/S	IP	16[a]	2
						N/S	IP	18[a]	
		SCID	HSC	Fetal liver	Unrelated	N/S	IV	28[a]	1
Westgren et al.[74]	N/A	SCID	HSC	Fetal liver	Unrelated	9.0×10^8 cells/kg, 7.0×10^7 cells total	IP	14	1
Westgren et al.[75]	N/A	α thalassaemia major	HSC	Fetal liver	Unrelated	2.04×10^9 cells/kg	IV	15	2
						1.2×10^8 cells/kg	IV	31	
		β thalassaemia major	HSC	Fetal liver	Unrelated	8.6×10^8 cells/kg	IV	18	1
		Sickle cell anemia	HSC	Fetal liver	Unrelated	1.67×10^9 cells/kg	IP	13	1
Westgren et al.[76]	N/A	Healthy	MSC	Fetal liver	Unrelated	2.5×10^7 cells total	IP	15	1
		Healthy	MSC	Fetal liver	Unrelated	3.8×10^7 cells total	IP	13	1
		Healthy	MSC	Fetal liver	Unrelated	2.9×10^7 cells total	IP	13	1
		Healthy	MSC	Fetal liver	Unrelated	2.4×10^7 cells total	IP	16	1
		Healthy	MSC	Fetal liver	Unrelated	2.9×10^7 cells total	IC	14	1
		Healthy	MSC	Fetal liver	Unrelated	1.3×10^7 cells total	IP	17	1
		Healthy	MSC	Fetal liver	Unrelated	8.5×10^7 cells total	IC	13	1
		Healthy	MSC	Fetal liver	Unrelated	8.5×10^7 cells total	IP	13	1
		Healthy	MSC	Fetal liver	Unrelated	2.7×10^7 cells total	IC	15	1
		Healthy	MSC	Fetal liver	Unrelated	2.8×10^7 cells total	IC	16	1

Note: Gestational age is presented in full weeks.

Abbreviations: CGD, Chronic Granulomatous Disease; HSC, haematopoietic stem cells; IP, intraperitoneal; IV, intravenous; SCID, Severe Combined Immunodeficiency.

[a]In these cases, gestational age was given in weeks post fertilization rather than in weeks post last menstrual period. In each of these cases 2 weeks has been added to the gestational age to make the values comparable to the other cases that reported gestational age post last menstrual period.

[b]In these cases, a cell dose/kg was stated, but it was not specified whether this was per injection or in total for both injections.

[c]All injections in this case series were reported as taking place between 21 and 25 weeks of gestation.

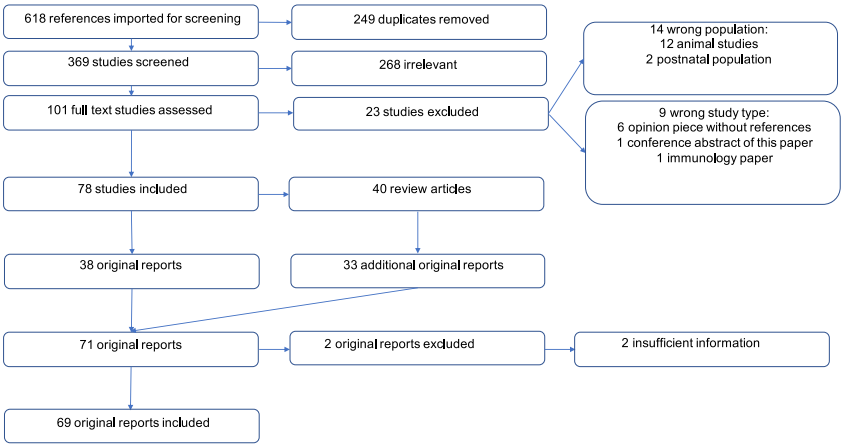

FIGURE 1 Flow diagram of study selection (adapted from PRISMA 2009). The electronic literature search identified 618 studies published from 1967 to 24/06/2023. 249 studies were removed as duplicates. The remaining studies (369) were screened by title and abstract, and a further 268 were excluded as irrelevant. Full texts of the remaining 101 articles were reviewed, and 23 were excluded for the following reasons: 14 wrong population (12 animal studies, 2 postnatal population) and 9 wrong study type (6 opinion pieces without references, 1 conference abstract of this systematic review study and 1 study on fetal immunology with no In utero stem cell transplantation (IUSCT)). 78 studies were identified based upon this initial search strategy. 38 publications were case reports/series of original data and were directly included. Forty review articles generated from the primary search were then reviewed independently by both reviewers and a secondary review of references performed. 33 additional studies detailing original cases were identified from this secondary review of references. Two publications detailing cases of IUSCT were excluded due to insufficient information. Eventually, 69 papers detailing 66 IUSCT procedures in 52 women were included in the final data set.

injections. Details pertaining to the congenital diseases treated, cell source, cell dose, gestational age at injection and injection type are in Supporting Information S1.

6 | ANALYSIS OF FETAL AND MATERNAL SAFETY OUTCOMES FOLLOWING IUSCT

We considered maternal and fetal outcomes separately at three timepoints (Table 2). Immediate post-procedural complications were defined as those which occurred during or within 48 h of the IUSCT injection procedure. The second timepoint considered was the remainder of the pregnancy and delivery. Finally, long-term outcomes after delivery were also considered.

6.1 | Immediate adverse events within 48 h of IUSCT

Of the 52 cases of IUSCT identified (66 injections), comments were found relating to the health of the fetus or pregnancy within 48 h of the IUSCT procedure in 36 cases; in 33 cases (39 injections) there were no reported concerns, whereas there were complications reported in three cases (4 injections). The presence or absence of immediate procedural complications within 48 h was not documented in 16 cases (23 injections). Only 16 cases (30.8%) contained a direct or implied reference to maternal health in the first 48 h of the procedure.

6.1.1 | Fetal/pregnancy outcomes

Two fetuses suffered a bradycardia and subsequently died in utero within 1 hour of the procedure. The first fetus was receiving a first intravenous injection of second trimester fetal liver-derived HSC for β thalassaemia major at 19 weeks of gestation.[52] The second fetus was undergoing a second intravenous injection of second trimester fetal liver-derived HSC for Chronic Granulomatous Disease at 23 weeks of gestation.[52] Fetal death during pregnancy, irrespective of cause, constitutes a Grade 5 fetal complication.[78]

One fetus undergoing transplantation of paternal bone marrow HSC intraperitoneally at 13 weeks for Globoid Cell Leukodystrophy was reported to have 'a small leakage of amniotic fluid' 1 hour following the procedure, with mild oligohydramnios noted on ultrasound. The following day, the liquor volume was reported to be normal, and no further leakage was reported. The fetus was later born alive at term.[26] The early gestational age at preterm prelabour rupture of the membranes (PPROM) could render a Grade 4 adverse event but as the oligohydramnios did not persist, the liquor-volume normalised and there was no change in management we therefore determined this was a Grade 2 adverse event.[78]

All three complications, two of which were Grade 5 fetal adverse events, were determined to be procedure related and were included in the descriptive statistics for acute procedure-related complications. Of the 66 IUSCT procedures, the acute per-procedure fetal complication rate was therefore 4.5% (3/66) and the acute procedural fetal mortality rate was 3% (2/66).

TABLE 2 Immediate, medium and long term maternal and fetal outcomes after in utero stem cell transplantation.

		Immediate		Pregnancy/Delivery				Long term				
Reference	Disease	Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/ immune response	GvHD	Tumorigenicity	Maternal
Fetuses who received HSC for red cell and clotting disorders												
Cowan and Golbus[11]	α thalassaemia major	Without any complications		Termination at 24 weeks- lack of engraftment, but the engraftment seen at PM	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
Hayward et al.[24]	α thalassaemia major	No evidence of fetal distress	N/S	Normal fetal growth on ultrasound, 2 in utero blood transfusions	N/S	N/S	36 weeks	Transfusion-dependent	Tolerant	N/S	N/S	N/S
McKenzie et al.[31]	α thalassaemia major	There were no unanticipated safety events in either mother/child pair		There were no unanticipated safety events in either mother/child pair, 4 in utero blood transfusions		N/S	N/S	Alive and well, transfusion-dependent	Tolerant, negative HLA antibodies	N/S	N/S	No SEs
	α thalassaemia major	There were no unanticipated safety events in either mother/child pair		There were no unanticipated safety events in either mother/child pair, 4 in utero blood transfusions		N/S	N/S	Alive and well, transfusion-dependent	Tolerant, negative HLA antibodies	N/S	N/S	No SEs
Westgren et al.[75]	α thalassaemia major	N/S	N/S	3 in utero blood transfusions at 29,32 and 35 weeks	N/S	CS	37 weeks	Transfusion-dependent, alive at aged 2 years	N/S	N/S	N/S	N/S
Orlandi et al.[35]	β thalassaemia major	N/S	N/S	N/S	N/S	N/S	N/S	Alive aged 2 years	Not tolerant	N/S	N/S	N/S
Renda and Maggio[45]	β thalassaemia major	No adverse events for fetus	No adverse events for mother	Normal fetal growth	The mother did not show any side effects	NVD	40 weeks	Transfusion-dependent	N/S	N/S	N/S	N/S
	β thalassaemia major	No adverse events for fetus	No adverse events for mother	Normal fetal development	The mother did not show any side effects	NVD	39 weeks	Transfusion-dependent	N/S	N/S	N/S	N/S
Sanna[48]	β thalassaemia major	N/S	N/S	Unevenful pregnancy, normal ultrasounds		N/S	Full term	Born with disease	Not tolerant	N/S	N/S	N/S
Slavin et al.[50]	β thalassaemia major	Procedure uneventful, No fetal distress		N/S	N/S	N/S	N/S	Correction not accomplished	N/S	No GvHD	N/S	N/S
Touraine et al.[52]	β thalassaemia major	No side effects of any kind in fetus	No side effects of any kind in mother	No side effects of any kind in fetus	No side effects of any kind in mother	N/S	37 weeks	Alive and well, partial effect on thalassaemia; became transfusion-dependent aged 5	Tolerant	No GvHD	N/S	N/S
Touraine et al.[52]	β thalassaemia major	Bradycardia and fetal death	N/S	N/A	N/A	N/A	N/A	N/A	N/S	N/S	N/S	N/S
Westgren et al.[75]	β thalassaemia major	Tolerated the procedure well	N/S	Pregnancy was uneventful		N/S	Term	Well, alive at 7 months and not transfusion-dependent	N/S	N/S	N/S	N/S
Davis[14]	Rh blood group alloimmunisation	N/S	N/S	3 in utero blood transfusions and 2 amniocentesis	Salpingitis at delivery and evidence of intrauterine infection	CS	32 weeks	Neonatal death on day 1 of life, congenital rubella	N/S	N/S	N/S	N/S
Linch et al.[29]	Rh blood group alloimmunisation	N/S	N/S	5 in utero blood transfusions	N/S	CS	33 weeks	Healthy	Not tolerant	N/S	N/S	N/S
Thilaganthan et al.[51]	Rh blood group alloimmunisation	N/S	N/S	6 in utero blood transfusions	N/S	CS	34 weeks	Healthy	Tolerant	No GvHD	N/S	N/S

TABLE 2 (Continued)

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/ immune response	GvHD	Tumorigenicity	Maternal
Westgren et al.[75]	Sickle cell anemia	Tolerated the procedure well	N/S	Pregnancy continued uneventfully		CS	Term	Born with disease and alive at age 1 year	N/S	N/S	N/S	N/S
Touraine et al.[52]	Hemophilia A	N/S	N/S	N/S	N/S	N/S	N/S	Well, no antifactor 8 antibodies	No factor 8 antibodies	N/S	N/S	N/S

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/immune response	GvHD	Tumorigenicity	Maternal
Fetuses who received HSC for immune disorders												
Touraine et al.[49]	Bare Lymphocyte Syndrome	No side effects of any kind in fetus	No side effects of any kind in mother	No side effects of any kind in fetus	No side effects of any kind in mother	NVD	37 weeks	T-cell reconstitution, received 7 postnatal stem cell transplants, well until BMT aged 11 died of CMV	Tolerant	No GvHD	N/S	N/S
Cowan and Golbus[11]	Chediack Higashi	N/S	N/S	N/S	N/S	N/S	Term	Required postnatal BMT, alive and well aged 1 year	Not tolerant	N/S	N/S	N/S
Flake and Zanjani[17]	CGD	N/S	N/S	N/S	N/S	N/S	N/S	Alive	N/S	N/S	N/S	N/S
Muench et al.[33]	CGD	N/S	N/S	Pregnancy without complications		N/S	38 weeks	Underlying disease	Not tolerant	N/S	N/S	N/S
Touraine et al.[52]	CGD	Bradycardia and fetal death	N/S	N/A	N/A	N/A	N/A	N/A	N/S	N/S	N/S	N/S
Cowan and Golbus[11]	SCID	N/S	N/S	Termination at 26 weeks- lack of engraftment	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
Flake et al.[15]	SCID	Well tolerated	N/S	Normal ultrasounds	N/S	CS	N/S	Healthy at 11 months	Tolerant	N/S	N/S	N/S
Magnani et al.[30]	SCID	No adverse events were observed during or after the cell infusion		The course of pregnancy was uneventful		N/S	Term	Healthy aged 36 months	N/S	No GvHD	N/S	N/S
Pirovano et al.[36]	SCID	Well tolerated by fetus	Well tolerated by mother	Normal fetal ultrasounds	No maternal engraftment	CS	38 weeks	Selective reconstitution of T and NK cell compartments	N/S	No GvHD	N/S	N/S
Pirovano et al.[1]	SCID	N/S	N/S	N/S	No maternal engraftment	N/S	N/S	Full cellular reconstruction	N/S	No GvHD	N/S	N/S
Pirovano et al.[36]	SCID	N/S	N/S	N/S	No maternal engraftment	N/S	N/S	10% T lymphocyte engraftment, severe lymphopenia, died aged 5 after BMT	N/S	No GvHD	N/S	N/S
Pirovano et al.[1]	SCID	N/S	N/S	N/S	No maternal engraftment	N/S	N/S	Full T and B cell reconstitution	N/S	No GvHD	N/S	N/S
Touraine et al.[52]	SCID	No side effects of any kind in fetus	No side effects of any kind in mother	No side effects of any kind in fetus	No side effects of any kind in mother	N/S	36 weeks	T-cell reconstitution died aged 9 after liver transplant for schlerosing cholangitis	Tolerant	No GvHD	N/S	N/S
Westgren et al.[74]	SCID	Tolerated the procedure well	N/S	The course of pregnancy and delivery have been uncomplicated		NVD	Term	Selective reconstitution of T and NK cell compartments, well aged 2 years	N/S	N/S	N/S	N/S

(Continues)

TABLE 2 (Continued)

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/immune response	GvHD	Tumorigenicity	Maternal
Pirovano et al.[36]	Omenn syndrome	N/S	N/S	Pregnancy uneventful		CS	37 weeks	Good reconstitution of the T cell line but needs immunoglobulin infusions	N/S	No GvHD	N/S	N/S

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/immune response	GvHD	Tumorigenicity	Maternal
Fetuses who received HSC for metabolic disorders												
Flake and Zanjani[17]	Hurler syndrome	N/S	N/S	N/S	N/S	N/S	N/S	Absent enzyme activity after 1 year died aged 2	N/S	N/S	N/S	N/S
Leung et al.[26]	Globoid cell leukodystrophy	Procedure uncomplicated, normal fetal heart rate		Intrauterine death after 7 weeks due to excessive infiltration	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Globoid cell leukodystrophy	FHR did not change, PPROM	N/S	Nomal fetal growth	N/S	CS	37 weeks	Born with disease and needed postnatal BMT	Not tolerant	N/S	N/S	N/S
	Globoid cell leukodystrophy	Procedure uncomplicated		Pregnancy uncomplicated		N/S	40 weeks	Born with disease, postnatal BMT planned	N/S	N/S	N/S	N/S
Slavin et al.[50]	Metachromatic leukodystrophy	Procedure uneventful, No fetal distress		N/S	N/S	N/S	N/S	Correction not accomplished	N/S	No GvHD	N/S	N/S
	Metachromatic leukodystrophy	Procedure uneventful, No fetal distress		N/S	N/S	N/S	N/S	Correction not accomplished	N/S	No GvHD	N/S	N/S
Touraine et al.[52]	Niemann Pick	No side effects of any kind in fetus	No side effects of any kind in mother	No side effects of any kind in fetus	Mother in excellent condition, No side effects of any kind in mother	N/S	40 weeks	Died of underlying condition at 22 months	N/S	N/S	N/S	N/S

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/immune response	GvHD	Tumorigenicity	Maternal
Fetuses who received MSC												
Götherström et al.[18]	OI	Normal fetal ultraound and heart rate	N/S	After normal ultrasounds, pregnancy was uneventful		CS	38 weeks	Better than predicted by genotype	No immune response to donor cells	N/S	N/S	N/S
	OI	No signs of fetal distress	N/S	Pregnancy was uncomplicated thereafter		CS	35 weeks	Better than predicted by genotype	No immune response to donor cells	N/S	N/S	N/S
Westgren et al.[76]	Healthy	All fetuses had normal fetal heart activity at the end of the procedure and were alive until at least 6 h before expulsion, with termination achieved 48–72h after administration	N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S

TABLE 2 (Continued)

Reference	Disease	Immediate		Pregnancy/Delivery				Long term				
		Fetal	Maternal	Pregnancy	Maternal health	Delivery	Gestational age	Fetal	Tolerance/immune response	GvHD	Tumorigenicity	Maternal
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S
	Healthy		N/S	N/A	N/S	N/A	N/A	N/A	N/S	N/S	N/S	N/S

Note: Highlighted in black are the cases of fetal loss, highlighted in dark gray are the cases with additional pregnancy complications, highlighted in light gray are the cases in which specific mention to maternal health was made.

Abbreviations: BMT, Bone marrow transplantation; CGD, Chronic Granulomatous Disease; CMV, Cytomegalovirus; CS, Caesarean section; FHR, fetal heart rate; N/A, Not applicable; N/S, Not specified; NVD, Normal vaginal delivery; OI, Osteogenesis Imperfecta; PPROM, preterm prelabour rupture of the membranes; SCID, Severe Combined Immunodeficiency; SE's, Side effects.

The 10 healthy fetuses who received IUSCT as part of a study of tissue distribution and concentrations of transplanted fetal liver cells in the human fetus all underwent planned termination of pregnancy 48–72 h following the procedure, as per the study protocol. All fetuses were documented as being alive 6 hour prior to termination.[76] These terminations were therefore not included within the complication rate and were not graded.

6.1.2 | Maternal outcomes

Maternal wellbeing in the first 48 h after the IUSCT procedure was documented in only 16 cases (30.8%). In seven of these, phrases such as 'the procedure was uncomplicated' have been interpreted as reporting both fetal and maternal wellbeing. Individual, specific mention of maternal wellbeing was found only in 9 cases of IUSCT (17.3%).

In the three cases where acute procedural complications were described, these are reported from the fetal perspective. For example, no report is given on the health of the mother in the two reported cases of fetal bradycardia and in utero fetal death.[52] Given the fetal gestation at demise of 19 and 23 weeks, respectively, the mother is likely to have been admitted to hospital for management of mid-trimester miscarriage, which would be a Grade 3 adverse event according to terminology.[78] Finally, in the pregnancy complicated by PPROM immediately following IUSCT at 13 weeks of gestation, the baby was delivered at term, meaning that severe maternal complications from the membrane rupture are unlikely.[26] This was defined as a Grade 2 maternal adverse event.[78]

In conclusion, no publications report details of maternal health or the specific maternal complications outside of the fetal complications already discussed. However, it is likely that at least one Grade 2 complication and two Grade 3 (or above) maternal complications related to the IUSCT procedure occurred.

6.2 | Pregnancy and delivery safety outcomes following IUSCT

From 48 h following the IUSCT procedure, there were 40 ongoing pregnancies. Seventeen cases were reported to have experienced no maternal or fetal complications, whilst a further two cases had no documented fetal complications. In the final four cases, it was documented only that there was no engraftment of cells in the pregnant woman. No information was provided about the remainder of the pregnancy in eight cases. In seven cases, there were further in utero procedures, all of which were fetal blood transfusion for fetal anemia due to α thalassaemia major ($n = 4$) or Rh blood group alloimmunisation ($n = 3$).[5, 11, 31, 79, 80] Both conditions are recognised to cause fetal anemia, requiring in utero blood transfusion in order to allow the pregnancy to progress to a viable gestation.[79] Indeed, the requirement for ongoing fetal blood transfusions was a pre-specified part of the trial of IUSCT in which two women were partaking.[31]

Therefore, we did not consider these subsequent in utero blood transfusions to be a complication of IUSCT.

6.2.1 | Fetal outcomes

Of the 40 continuing pregnancies, three fetuses died before birth. Two pregnancies, one in which the fetus was affected by α thalassaemia major and one with SCID, were terminated when fetal blood samples showed no evidence of engraftment of maternal bone marrow HSC.[80] At postmortem examination, one of these fetuses showed evidence of engraftment.[11] We did not include these deaths in the mortality rate attributed to IUSCT. One fetus who received paternal bone marrow HSC intraperitoneally at 13 weeks for globoid cell leukodystrophy died in utero at 20 weeks of gestation due to "excessive infiltration", death which should be considered directly related to IUSCT and included as a Grade 5 fetal complication.[26] The cell dose given was 5.0×10^9 cells/kg. Two further fetuses with the same condition underwent similar IUSCT treatment but received a ten-fold lower cell dose, with no reports of similar complications during the pregnancies.[26]

Of 37 fetuses surviving to birth, gestational age at delivery was reported in 24 cases; 18 fetuses were born at term, whilst 6 were born preterm at gestations between 32 and 36 weeks. All three fetuses who received IUSCT for Rh blood group alloimmunisation were delivered preterm, as was one of the fetuses who received IUSCT for α thalassaemia major.[5, 24, 51, 81] It is likely that the preterm deliveries in these cases were due to the underlying congenital disorder; it is standard practise to deliver a fetus with a need for ongoing transfusions once a late preterm gestation is reached, usually between 34 and 36 weeks of gestation, in preference to performing further in utero transfusions.[9, 82, 83]

A fetus who received one intravenous infusion of fetal liver HSC at 28 weeks for SCID was delivered at 36–37 weeks of gestation.[52] Finally, a fetus who received an uncomplicated intravenous IUSCT of fetal liver MSC for OI at 32 weeks of gestation was delivered at 35 weeks after spontaneous PPROM occurred.[18, 19] The study authors concluded that the preterm delivery 3 week after the procedure was due to the fetus' underlying disease as this is associated with a high rate of preterm birth.[84] Thus, these occurrences of preterm delivery were not included in the complication rate.

There was one neonatal death.[5] This was a complicated case where bone marrow HSC had been given to the fetus via hysterotomy at 11 weeks of gestation for Rh blood group alloimmunisation. Five further needling procedures occurred during the pregnancy: twice to perform amniocentesis and three times for in utero blood transfusion. The pregnancy was complicated by PPROM following a fetal transfusion at 26 weeks, vaginal bleeding, and spontaneous preterm labor at 32 weeks. During the last blood transfusion at 31 weeks of gestation, the needle was seen to enter the fetal bowel. The baby died on day one of life after developing respiratory distress and signs of infection. After delivery, there was evidence that the fetal anemia may have been caused by congenital rubella infection and that the fetus may have been the Rh blood group negative. There was additional post-mortem evidence of fetal bowel perforation and meconium peritonitis, which corresponded to the complications of the fetal blood transfusion at 31 weeks. Whilst this constituted a grade 4 intraoperative injury adverse event as the unintended damage to the fetal organ was life-threatening, these complications are undoubtedly a result of the last intrauterine blood transfusion needling procedure at 31 weeks. We therefore considered it unlikely that the complications were related to IUSCT, which took place at 11 weeks of gestation.[78]

Overall, 71.2% (37/52) of fetuses who received IUSCT survived to delivery, and 69.2% (36/52) survived to the end of the neonatal period. With terminated pregnancies removed, neonatal survival was 90% (36/40). The mortality rate related to IUSCT during pregnancy was 7.5% (3/40), whereas the complication rate attributed to IUSCT during pregnancy was 10% (4/40).

6.2.2 | Maternal outcomes

Maternal outcomes during the remainder of the pregnancy or at delivery were specifically stated in 13 (25%) cases and implied from phrases such as 'uncomplicated pregnancy' in an additional 10 cases (44.2% overall). As was the case for immediate complications, in the cases complicated by adverse fetal outcomes or by further in utero procedures, maternal health were generally not reported. Of the eight complicated cases (repeated in utero blood transfusions ($n = 7$) and intrauterine death due to 'overwhelming engraftment' ($n = 1$)), the maternal outcome was documented in only three cases.[5, 31] In two of these cases, the mother was well during a follow-up, up to a year after delivery. In the other case, however, the mother is described as having evidence of salpingitis at delivery. This maternal complication is likely unrelated to the IUSCT procedure performed over 20 weeks prior, but if thought related to the IUSCT would constitute a Grade 2 maternal adverse event.[5]

We considered the requirement for in utero blood transfusions in the additional four cases to be related to the underlying disorder and thus not related to the IUSCT. However, in the case of intrauterine demise secondary to overwhelming engraftment, a complication caused by IUSCT, the resulting mid-trimester management of miscarriage is likely to have required hospital admission, which would constitute a Grade 3 maternal adverse event.

6.3 | Long term outcomes of IUSCT

6.3.1 | Fetal outcomes

Of the 36 surviving fetal recipients of IUSCT, there was evidence of benefit in 12 cases, and possible benefit in two additional cases. These long term outcomes have been extensively discussed elsewhere, and are not analyzed in this systematic review of fetal and

maternal safety.[85] Further details are available in Supporting Information S1.

Recipient safety reporting was inconsistent and poorly reported across papers. Common concerns relating to the safety of stem cell transplantation are those surrounding the immune response or potential tumorigenicity. Immunological tolerance or a lack of immune response toward donor antigens was reported in 11 cases, whilst 6 cases were reported to be non-tolerant of donor cells. Thirteen cases reported no evidence of Graft versus Host disease, whilst no papers reported any evidence of tumorigenicity.

6.3.2 | Maternal outcomes

Long term maternal outcomes following delivery were very poorly reported with maternal wellbeing only specifically documented in two cases, both participants in a recent trial of maternal and fetal safety of IUSCT.[31]

7 | COMMENT

This systematic review of cases of IUSCT identified 69 publications describing 66 procedures in 52 pregnancies from 1967 to present. Of the included cases, there was great heterogeneity in terms of indication for transplantation, cell source and dose given, the route of injection and gestational age at procedure. These cases have been published by many different authors, using disparate protocols, over a long period of time. A limitation of this systematic review is that the small number of published cases has necessitated grouping together all cases of IUSCT to attempt to draw conclusions, event those which took place half a century ago.

A second limitation of this review is that at least 14 additional cases of IUSCT were found in the literature, but insufficient information to analyze and include. It is therefore likely that more unpublished attempts have taken place, and these results may be subject to publication bias.

The acute fetal complication rate during and in the 48 h following the IUSCT procedure was 4.5% (3/66), all of which occurred in cases published prior to 1994. Considerable technical improvements have taken place during the intervening 28 years both in terms of ultrasound resolution and procedural advances in *in utero* needling techniques. As an example, the largest cohort study of in utero blood transfusions reports the fetal outcome of 1678 blood transfusion procedures performed in the Netherlands over this general time period.[9] 741 of these procedures were performed prior to 2001, with a per-procedure complication rate of 3.1%, and a mortality rate of 1.6%. A retrospective safety analysis was performed and after implementation of practise improvement points, such as routinely using fetal paralysis, and avoiding injection into free cord loops, 937 procedures were subsequently performed. In this second cohort of patients treated from 2001 to 2015, the authors report a procedure complication rate of 1.2% and a procedure loss rate of 0.6%. It is therefore likely that IUSCT procedures, performed today and using the knowledge from these best practise points from fetal blood transfusion studies, will have a lower procedure related complication rate than was seen in cases carried out 3 decades ago.

There was one IUSCT-related fetal complication reported in the intermediate term, which the authors attribute to a direct fetal reaction to the high cell dose given, as subsequent use of a ten-fold lower dose of cells in two fetuses was not related to similar complications.[26] For long term fetal outcomes, the majority of reports focused on efficacy rather than on reporting safety parameters. There was convincing evidence of benefit in 10 cases of immunodeficiency (HSC) and two cases of OI (MSC), with partial benefit in two cases of thalassaemia. There was no demonstrable benefit in storage diseases or clotting disorders. These cases have been discussed in detail elsewhere and further comment is outside the scope of this review. Whilst non-tolerance to donor cells was reported in some cases, there were no reports of immune response, GvHD, or tumorigenicity in any of the fetal recipients, and no reported direct long-term complications.

Maternal outcomes were less well reported than fetal. In only nine cases was it specifically documented that there were no acute procedural complications in the mother. Likewise, only 13 cases specifically mention maternal wellbeing during pregnancy and delivery. An additional 10 publications made general comments about there being no complications during pregnancy, which has been interpreted as stating that there were no maternal or fetal complications (44.2% overall). There are only two reports of maternal health after delivery of the baby; in both cases the mothers were well a year following delivery. This lack of explicit maternal safety reporting is not unique to IUSCT and has, for example, been commented upon in a recent systematic review of fetal surgery for spina bifida.[86]

Whilst there were no specific maternal-only complications related to IUSCT reported in the 52 pregnant women studied in this systematic review, in three cases which reported acute or intermediate fetal/pregnancy related complications, it is likely that the complication would have additionally constituted at least a grade 3 maternal adverse event according to MFAET taxonomy.

Despite the poor reporting of safety outcomes overall, certain conclusions can reasonably be drawn from our results. Three of the four fetal complications related directly to IUSCT occurred within 24 h of the IUSCT procedure. This time course is consistent with the complications which were reported to occur after in utero blood transfusion by Zwiers et al, where seven of the 11 documented procedure related complications (in 334 fetuses) occurred within 24 h of the IUT procedure.[9] We therefore recommend that monitoring for adverse events should focus most on the 24–48 h immediately following IUSCT. However, one intrauterine death directly related to IUSCT occurred 7 weeks following the procedure; hence, we recommend that monitoring takes place throughout the pregnancy and delivery. Very little data is available regarding long-term safety of IUSCT, and for this reason, we recommend long-term follow-up in order to establish reliable safety data. Certainly,

competent authorities require that trials investigating the administration of advanced therapy medicinal products such as stem cells follow-up participants for minimum 5 years.[87] Tumorigenicity and immune response are pertinent negatives to report in the long-term follow-up.

Reporting the presence or absence of not only fetal but also neonatal and maternal complications is recommended in future cases of IUSCT. Indeed, adverse event reporting for all studies involving pregnant women should use maternal and fetal definitions and grades according to MFAET, which has been mapped to MedDRA and for neonates should use the National Cancer Institute INC Neonatal Adverse Events Terminology (NAESS).[88, 89]

Given the limited evidence available currently to support the safety and efficacy of IUSCT, we recommend that it should take place only in the setting of clinical trials, where safety is recorded as the primary outcome, and with fetal, maternal and neonatal outcomes documented in the immediate, medium and long term according to accepted clinical trial definitions. Subsequently, should both safety and efficacy be demonstrated for IUSCT for a given condition, IUSCT could then be performed as a standard of care according to best practise protocols developed during these trials.

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CONFLICT OF INTEREST STATEMENT

Lilian Walther-Jallow, Cecilia Götherström and Magnus Westgren are co-founders of BOOST Pharma ApS, and Lilian Walther-Jallow is employed by BOOST part-time.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

Ethical approval was not required as this study is a systematic review that used only previously published data.

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REFERENCES

1. Pirovano S, Notarangelo L, Valotti M, et al. Mutations of the T-cell receptor constant region after in utero stem cell transplantation. *Immunogenetics*. 2004;56(3 PG-214–9):214-219. https://doi.org/10.1007/s00251-004-0680-3
2. Campagnoli C, Roberts IA, Kumar S, Bennett PR, Bellantuono I, Fisk NM. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. *Blood*. 2001;98(8):2396-2402. https://doi.org/10.1182/blood.v98.8.2396
3. Erkers T, Kaipe H, Nava S, et al. Treatment of severe chronic graft-versus-host disease with decidual stromal cells and tracing with (111) indium radiolabeling. *Stem Cells Dev*. 2015;24(2):253-263. https://doi.org/10.1089/scd.2014.0265
4. Hill M, Lewis C, Riddington M, et al. Stakeholder views and attitudes towards prenatal and postnatal transplantation of fetal mesenchymal stem cells to treat Osteogenesis Imperfecta. *Eur J Hum Genet*. 2019;27(8):1244-1253. https://doi.org/10.1038/s41431-019-0387-4
5. Davis J. *Clinicopathological Conference. A Case of Haemolytic Disease with Congenital Rubella Demonstrated at the*. Royal Postgraduate Medical School; 1967.
6. Touraine J. In utero transplantation of stem cells in humans. *Nouv Rev Fr Haematol*. 1990;32:441-444.
7. Le Blanc K, Chan Ewald JK, Fisk NM, et al. Osteogenesis imperfecta: a two-center experience pre-and postnatal transplantation of fetal mesenchymal stem cells in pre-and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfecta: a two-center experience. *Stem Cells Transl Med*. 2014;3:1-10.
8. Le Blanc K, Gotherstrom C, Ringden O, et al. Mesenchymal stem cell engraftment in bone following in utero transplantation in a patient with severe osteogenesis imperfecta. *Blood*. 2004;104(11 PG-147A-147A):147A.
9. Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. *Ultrasound Obstet Gynecol*. 2017;50(2):180-186. https://doi.org/10.1002/uog.17319
10. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(1):b2535. https://doi.org/10.1136/bmj.b2535
11. Cowan MJ, Golbus M. In utero hematopoietic stem cell transplants for inherited diseases. *Am J Pediatr Hematol Oncol*. 1994;16(1):35-42.
12. Diukman R, Golbus MS. In utero stem cell therapy. *Journal of Reproductive Medicine for the Obstetrician and Gynecologist*. 1992;37:515-520.
13. Golbus M. RAC hears review of in utero stem cell transplant, gene therapy. *Biotechnol Law Rep*. 1996;15(2 PG-208):208.
14. Davis J. Clinicopathological conference. A case of haemolytic disease with congenital rubella demonstrated at the Royal Postgraduate Medical School. *Br Med J*. 1967;2:819-822.
15. Flake AW, Roncarolo MG, Puck JM, et al. Treatment of X-linked Severe Combined Immunodeficiency by in utero transplantation of paternal bone marrow. *N Engl J Med*. 1996;335(24):1806-1810. https://doi.org/10.1056/nejm199612123352404
16. Zanjani ED, Almeida-Porada G, Porada C, Flake AW. In utero approach to hematopoietic stem cell transplantation. *Correction of Genetic Diseases by Transplantation Iv*. 1997:137-150.
17. Flake AW, Zanjani ED. In utero hematopoietic stem cell transplantation: ontogenic opportunities and biologic barriers. *Blood*. 1999;94(7):2179-2191. https://doi.org/10.1182/blood.v94.7.2179.419k43_2179_2191
18. Götherström C, Westgren M, Shaw SWS, et al. Pre- and postnatal transplantation of fetal mesenchymal stem cells in osteogenesis imperfecta: a two-center experience. *Stem Cells Transl Med*. 2014;3(2):255-264. https://doi.org/10.5966/sctm.2013-0090
19. Le Blanc K, Gotherstrom C, Ringdén O, et al. Fetal mesenchymal stem-cell engraftment in bone after in utero transplantation in a patient with severe osteogenesis imperfecta. *Transplantation*. 2005;79(11):1607-1614. https://doi.org/10.1097/01.tp.0000159029.48678.93

20. Westgren L, Anneren G, Axelsson O, Evald U, LeBlanc K, Ringden O. Donor chimerism across full allogenic barriers acheived by in utero transplantation of fetal mesenchymal stem cells in a case of osteogenesis imperfecta. *Am J Obstet Gynecol*. 2003;189(6):s215. https://doi.org/10.1016/j.ajog.2003.10.575
21. Westgren M, Westgren M. In utero stem cell transplantation. *Semin Reprod Med*. 2006;24(5):348-357. https://doi.org/10.1055/s-2006-952156
22. Chan JKY, Gotherstrom C. Prenatal transplantation of mesenchymal stem cells to treat osteogenesis imperfecta. *Front Pharmacol*. 2014;5:223. https://doi.org/10.3389/fphar.2014.00223
23. Götherström C, Le B, Aestrom E, et al. Ten years follow up after prenatal transplantation of fetal mesenchymal stem cell in a patient with severe osteogenesis imperfecta. *Bone Abstr*. 2013. https://doi.org/10.1530/boneabs.1.pp1
24. Hayward A, Ambruso D, Battaglia F, et al. Microchimerism and tolerance following intrauterine transplantation and transfusion for α-thalassemia-1. *Fetal Diagn Ther*. 1998;13(1):8-14. https://doi.org/10.1159/000020793
25. Eddleman K. In utero transfusion and transplantation in α-thalassaemia. In: Migliaccio AR, ed. *Stem Cell Therapy of Inherited Disorders*; 1996.
26. Leung W, Blakemore K, Jones RJ, et al. A human-murine chimera model for in utero human hematopoietic stem cell transplantation. *Biol Blood Marrow Transpl*. 1999;5(1):1-7. https://doi.org/10.1053/bbmt.1999.v5.pm10232735
27. Bambach BJ, Moser HW, Blakemore K, et al. Engraftment following in utero bone marrow transplantation for globoid cell leukodystrophy. *Bone Marrow Transpl*. 1997;19(4):399-402. https://doi.org/10.1038/sj.bmt.1700665
28. Blakemore KJ, Bambach BJ, Moser HW. Engraftment following in utero bone marrow transplantation for globoid cell leukodystrophy. *Am J Obstet Gynecol*. 1996.
29. Linch DC, Rodeck CH, Nicolaides K, Jones HM, Brent L. Attempted bone marrow transplantation in a 17 week fetus. *Lancet*. 1986;328(8521–8522):1453. https://doi.org/10.1016/s0140-6736(86)92754-6
30. Magnani A, Jouannic J.-M, Rosain J, et al. Successful in utero stem cell transplantation in X-linked severe combined immunodeficiency. *Blood Adv*. 2019;3(3):237-241. https://doi.org/10.1182/bloodadvances.2018023176
31. MacKenzie TC, Frascoli M, Sper R, et al. In utero stem cell transplantation in patients with alpha thalassemia major: interim results of a phase 1 clinical trial. *Blood*. 2020;136(Suppl 1):1. https://doi.org/10.1182/blood-2020-142698
32. Lianoglou BR, Gonzalez V, Velez JG, et al. 458: impact of in utero transfusions in fetuses with hydrops fetalis due to alpha thalassemia. *Am J Obstet Gynecol*. 2020;222(1):S300-S301. https://doi.org/10.1016/j.ajog.2019.11.474
33. Muench MO, Rae J, Bárcena A, et al. Transplantation of a fetus with paternal Thy-1+ CD34+ cells for chronic granulomatous disease. *Bone Marrow Transpl*. 2001;27(4):355-364. https://doi.org/10.1038/sj.bmt.1702798
34. Harrison. Allogeneic in utero transplantation of CD34 + THY-1 + bone marrow derived hematopoietic stem cells (HSC) in a fetus with chronic granulomatous disease. In: *Proceedings of the International Fetal Medicine and Surgery Society UK*. Carlisle; 1999.
35. Orlandi F, Giambona A, Messana F, et al. Evidence of induced non-tolerance in HLA-identical twins with hemoglobinopathy after in utero fetal transplantation. *Bone Marrow Transpl*. 1996;18(3):637-639.
36. Pirovano S, Notarangelo LD, Malacarne F, et al. Reconstitution of T-cell compartment after in utero stem cell transplantation: analysis of T-cell repertoire and thymic output. *Haematologica*. 2004;89(4):450-461.
37. Porta F, Easton J, Caldiani k. Bone marrow transplantation in utero: report of 5 cases affected by severe combined immunodeficiency. *Bone Marrow Transplant*. 2003;31(S63).
38. Porta F, Mazzolari E, Zucca S. Prenatal transplant in a fetus affected by Omenn syndrome. *Bone Marrow Transpl*. 2000;25:s43.
39. Bartolomé J, Porta F, Lafranchi A, et al. B cell function after haploidentical in utero bone marrow transplantation in a patient with severe combined immunodeficiency. *Bone Marrow Transpl*. 2002;29(7):625-628. https://doi.org/10.1038/sj.bmt.1703410
40. Gil J, Porta F, Bartolomé J, et al. Immune reconstitution after in utero bone marrow transplantation in a fetus with severe combined immunodeficiency with natural killer cells. *Transpl Proc*. 1999;31(6):2581. https://doi.org/10.1016/s0041-1345(99)00510-2
41. Lanfranchi A, Neva A, Tettoni K, Veradi r, Mazzolari E, Wengler GS. In utero transplantation (IUT) of parental CD34 + cells in patient affected by primary immunodeficiencies. *Bone Marrow Transpl*. 1998;21:S127.
42. Lanfranchi A, Porta F, Chirico G. Stem cells and the frontiers of neonatology. *Early Hum Dev*. 2009;85(10):S15-S18. https://doi.org/10.1016/j.earlhumdev.2009.08.005
43. Wengler GS, Lanfranchi A, Frusca T, et al. In-utero transplantation of parental CD34 haematopoietic progenitor cells in a patient with X-linked severe combined immunodeficiency (SCIDXI). *Lancet (London, Engl*. 1996;348(9040):1484-1487. https://doi.org/10.1016/s0140-6736(96)09392-0
44. Ugazio A, Lanfranchi A, Tettoni K, Porta F. Intrauterine stem cell transplantantion for severe combined immunodeficiencies. 1999;8:49-67.
45. Renda MC, Maggio A. In utero haematopoietic stem cell transplantation (IUHSCT). *Mediterr J Hematol Infect Dis*. 2009;1(1 PG-e2009031):e2009031. https://doi.org/10.4084/mjhid.2009.031
46. Renda MC, Damiani G, Fecarotta E, et al. In utero stem cells transplantation after a mild immunosuppression: evidence of paternal ABO cDNA in β-thalassaemia affected fetus. *Blood Transfus*. 2005;3(1):55-65.
47. Renda MC, Fecarotta E, Maggio A, et al. In utero fetal liver hematopoietic stem cell transplantation: is there a role for alloreactive T lymphocytes? *Blood Transfus*. 2000;96(4):1608-1609. https://doi.org/10.1182/blood.v96.4.1608.h8001608a_1608_1609
48. Sanna M. In utero stem cell transplantation for beta-thalassemia: a case report. *Bone Marrow Transpl*. 1999;23:S109.
49. Monni G, Ibba RM, Zoppi MA, Floris M. In utero stem cell transplantation. *Croat Med J*. 1998;39(2 PG-220–3):220-223.
50. Slavin S, Naparstek E, Ziegler M, Lewin A. Clinical application of intrauterine bone marrow transplantation for treatment of genetic diseases - feasibility studies. *Bone Marrow Transplant*. 1992:189-190.
51. Thilaganthan B, Nicolaides KH, Morgan G. Intrauterine bone-marrow transplantation at 12 weeks' gestation. *Lancet Jul*. 1993;24(8865):243. https://doi.org/10.1016/0140-6736(93)92336-r
52. Touraine J.-LL, Raudrant D, Golfier F, et al. Reappraisal of in utero stem cell transplantation based on long-term results. *Fetal Diagn Ther*. 2004;19(4):305-312. https://doi.org/10.1159/000077957
53. Raudrant D, Touraine JL, Rebaud A. In utero transplantation of stem cells in humans: technical aspects and clinical experience during pregnancy. *Bone Marrow Transpl*. 1992;9(Suppl 1):98-100.
54. Touraine JL. Stem cell transplantation in primary immunodeficiency, with special reference to the first prenatal, in utero, transplants. *Allergol Immunopathol*. 1991;19(2):49-51.
55. Touraine JL, Raudrant D, Vullo C, et al. New developments in stem cell transplantation with special reference to the first in utero transplants in humans. *Bone Marrow Transpl*. 1991;7(Suppl 3):92-97.
56. Touraine JL, Raudrant D, Royo C, et al. In utero transplantation of hemopoietic stem cells in humans. *Transpl Proc*. 1991;23(1 Pt 2):1706-1708.

57. Touraine J. In utero transplantation of fetal liver stem cells in humans. *Blood Cell*. 1991;17(2):379-387.
58. Touraine JL. The fetal liver as a source of stem cells for transplantation into fetuses in utero. *Curr Top Microbiol Immunol*. 1992;177:187-193.
59. Touraine JL. In-utero transplantation of fetal liver stem cells into human fetuses. *Hum Reprod*. 1992;7(1):44-48. https://doi.org/10.1093/oxfordjournals.humrep.a137554
60. Touraine J, Raudrant D, Rebaud A, et al. In utero transplantation of stem cells in humans: immunological aspects and clinical follow-up of patients. *Bone Marrow Transpl*. 1992;9(Suppl 1):121-126.
61. Touraine JL. Rationale and results of in utero transplants of stem cells in humans. *Bone Marrow Transpl*. 1992;10(Suppl 1):121-126.
62. Touraine JL. Transplantation of fetal liver stem cells into patients and into human fetuses, with induction of immunologic tolerance. *Transpl Proc*. 1993;25(1 Pt 2):1012-1013.
63. Touraine JL. In utero fetal liver cell transplantation in the treatment of immunodeficient or thalassemic human fetuses. *Transfus Sci*. 1993;14(3):299-304. https://doi.org/10.1016/0955-3886(93)90013-k
64. Touraine J. In utero transplantation of fetal liver stem cells into human fetuses for immunodeficiency and thalassemia treatment. In: *Gluckman E Colombel eds Ontogeny of Haematopoiesis*; 1995:169-176.
65. Touraine J.-L. Treatment of human fetuses and induction of immunological tolerance in humans by in utero transplantation of stem cells into fetal recipients. *Acta Haematol*. 1996;96(3):115-119. https://doi.org/10.1159/000203741
66. Touraine J. In utero transplantation of fetal liver stem cells into human fetuses. *J Hematother*. 1996;5(2):195-199. https://doi.org/10.1089/scd.1.1996.5.195
67. Touraine JL. Induction of transplantation tolerance in humans using stem cell transplants prenatally or postnatally. *Transpl Proc*. 1999;31(7):2735-2737. https://doi.org/10.1016/s0041-1345(99)00545-x
68. Touraine JL, Raudrant D, Laplace S, Gebuhrer L. Stem cell transplants in utero for genetic diseases: treatment and a model for induction of immunologic tolerance. *Transpl Proc*. 1999;31(1–2):681-682. https://doi.org/10.1016/s0041-1345(98)01606-6
69. Touraine J.-L. Stem cell transplantation in utero for genetic diseases. *Transpl Proc*. 2001;33(1–2):1750-1751. https://doi.org/10.1016/s0041-1345(00)02665-8
70. Touraine J, Raudrant D, Royo C, et al. IN-UTERO transplantation of stem cells in bare lymphocyte syndrome. *Lancet*. 1989;333(8651):1382. https://doi.org/10.1016/s0140-6736(89)92819-5
71. Touraine JL, Roncarolo MG, Plotnicky H, et al. *Tolerance to alloantigen's and recognition for allo + x induced in humans by fetal stem cell transplantation*. Vol 25. Rejection and Tolerance. Springer Netherlands; 1994:265-277.
72. Touraine JL, Raudrant D, Laplace S, Roncarolo MG. Immunological tolerance following stem cell transplantation in human fetuses in utero. *Transpl Proc*. 1997;29(5):2477. https://doi.org/10.1016/s0041-1345(97)00455-7
73. Touraine J, Raudrant D, Laplace S. Transplantation of hemopoietic cells from the fetal liver to treat patients with congenital diseases postnatally or prenatally. *Transpl Proc*. 1997;29(1–2):712-713. https://doi.org/10.1016/s0041-1345(96)00432-0
74. Westgren M, Ringdén O, Bartmann P, et al. Prenatal T-cell reconstitution after in utero transplantation with fetal liver cells in a patient with X-linked severe combined immunodeficiency. *Am J Obstet Gynecol*. 2002;187(2):475-825. https://doi.org/10.1067/mob.2002.123602
75. Westgren M, Ringden O, Eik-Nes S, et al. Lack of evidence of permanent engraftment after in utero fetal stem cell transplantation in congenital hemoglobinopathies. *Transplantation*. 1996;61(8 PG-1176–9):1176-1179. https://doi.org/10.1097/00007890-199604270-00010
76. Westgren M, Ek S, Bui T, et al. Tissue distribution of transplanted fetal liver cells in the human fetal recipient. *Am J Obstet Gynecol*. 1997;176(1 Pt 1):49-53. https://doi.org/10.1016/s0002-9378(97)80010-5
77. Mapping. MedDRA [Internet]; 2023. https://www.meddra.org/mapping
78. Spencer RN, Hecher K, Norman G, et al. Development of standard definitions and grading for maternal and fetal adverse event terminology. *Prenat Diagn*. 2022;42(1):15-26. https://doi.org/10.1002/pd.6047
79. Lindenburg ITM, van Kamp IL, Oepkes D. Intrauterine blood transfusion: current indications and associated risks. *Fetal Diagn Ther*. 2014;36(4):263-271. https://doi.org/10.1159/000362812
80. Cowan MJ, Golbus M, Mj. C MG. In utero hematopoietic stem cell transplants for inherited diseases. *Am J Pediatr Hematol Oncol*. 1994;16(1 PG-35–42):35-42.
81. Linch DC, Rodeck CH, Nicolaides K, Jones HM, Brent L. Attempted bone-marrow transplantation in a 17-WEEK fetus. *Lancet*. 1986;328(8521–8522):1453. https://doi.org/10.1016/s0140-6736(86)92754-6
82. Sainio S, Nupponen I, Kuosmanen M, et al. Diagnosis and treatment of severe hemolytic disease of the fetus and newborn: a 10-year nationwide retrospective study. *Acta Obstet Gynecol Scand*. 2015;94(4):383-390. https://doi.org/10.1111/aogs.12590
83. Guilbaud L, Garabedian C, Cortey A, Rakza T, Carbonne B, Houfflin-Debarge V. In utero treatment of severe fetal anemia resulting from fetomaternal red blood cell incompatibility: a comparison of simple transfusion and exchange transfusion. *Eur J Obstet Gynecol Reprod Biol*. 2016;201:85-88. https://doi.org/10.1016/j.ejogrb.2016.03.037
84. Yimgang DP, Brizola E, Shapiro JR. Health outcomes of neonates with osteogenesis imperfecta: a cross-sectional study. *J Matern Neonatal Med*. 2016;29(23):3889-3893. https://doi.org/10.3109/14767058.2016.1151870
85. Tiblad E, Westgren M, Tiblad E, Westgren M. Fetal stem-cell transplantation. *Best Pract Res Clin Obstet Gynaecol*. 2008;22(1):189-201. https://doi.org/10.1016/j.bpobgyn.2007.07.007
86. Sacco A, van der Veeken L, Bagshaw E, et al. Maternal complications following open and fetoscopic fetal surgery: a systematic review and meta-analysis. *Prenat Diagn*. 2019;39(4):251-268. https://doi.org/10.1002/pd.5421
87. Guideline EMA. On safety and efficacy follow-up - risk management of Advanced Therapy. *Medicinal Products*. 2008;44:1-18.
88. Salaets T, Turner MA, Short M, et al. Development of a neonatal adverse event severity scale through a Delphi consensus approach on behalf of the International Neonatal Consortium. *Arch Dis Child*. 2019;0:1-7.
89. International Neonatal Consortium (INC). Terminology Files [Internet]; 2023. https://evs.nci.nih.gov/ftp1/Pediatric_Terminologies/INC/About.html

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