High Incidence of Contaminating Maternal Cell Overgrowth in Human Placental Mesenchymal Stem/Stromal Cell Cultures: A Systematic Review

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INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are under investigation in more than 200 clinical trials [1], not just for cell replacement and tissue engineering applications, but also for their immunomodulatory, anti-inflammatory, angiogenic, and antiapoptotic effects in tissue repair. MSCs are heterogeneous populations of multipotent progenitor cells that can differentiate into mesenchymal lineages of fat, bone, muscle, and cartilage ex vivo and that preferentially migrate to sites of inflammation and injury after systemic delivery [2–4]. Their transplantability across major histocompatibility complex barriers without the need for immune suppression enables their cryopreservation as an allogeneic “off-the-shelf” cell therapy for use in acute or chronic medical settings.

Mesenchymal stromal cells derived from the fetus and its related placental/adrenal tissues display ontological properties that may be advantageous compared with their adult counterparts for clinical translation. This is supported by studies that have reported MSCs isolated from fetal blood, liver, or bone marrow to have greater expansion capacity, to have faster doubling times, to exhibit greater immunosuppressive properties, and to have arguably broader multipotentiality than adult MSCs [5–8], for example, in vitro into skeletal muscle [9], endothelium [10], oligodendrocytes [11], and cardiac lineage cells [12]. Similarly, MSCs isolated from placenta have been reported to differentiate in vitro into cells expressing skeletal, neural, and hepatocyte markers [13, 14]. These placental studies assume that such cultured MSC populations are fetal but do not address the possibility of maternal contamination. Thus, although fetoplacental MSCs have been viewed favorably as candidates for use in regenerative medicine, tissue engineering, and gene therapy, including for pre- and postnatal transplantation [15], more analysis is needed to understand the impact of gestational age and/or anatomical source.

The placenta, consisting mostly of trophoblast or chorionic villi, is an abundant source of fetal-derived cells. Indeed, chorion villus sampling for prenatal diagnosis is based on this...
premise. However, maternal decidual tissue is in close contact with the chorion at the basal plate, and decidual MSCs have been cultured from uterine scrapings, decidua parietalis, and basal chori- rionic membrane [7, 16, 17]. Because decidua may invaginate into placental cotyledons, protocols have been developed to obviate maternal cell contamination at chorionic villus sampling [18, 19]. For similar reasons, the First International Workshop on Placenta Derived Stem Cells recommended that cells isolated from placental tissue should be assessed for fetal origin using methods sensitive enough to exclude maternal contamination of ≤ 1% [20]. Despite this, conflicting reports have emerged regarding the origin of MSCs from placental chorionic tissue [21, 22]. In particular, a number of studies attest to pure or predominantly maternal-origin MSC cultures derived from this tissue, and indeed clinical trials are under way in relation to “placental MSCs” of maternal origin [23–26].

Establishing the prevalence of maternal contamination has clear implications for the robustness and validity of both preclinical studies and clinical trials using placental MSCs. Accordingly, we undertook a systematic review of studies investigating human placental and/or chorionic MSCs to determine (a) the frequency and purity of maternal contamination in cultured placental chorionic MSC populations and (b) clinical and laboratory correlates associated with maternal contamination.

**MATERIALS AND METHODS**

**Data Sources**

The search strategy was developed in accordance with the Center for Reviews and Dissemination’s Guidance for Systematic Reviews in Health Care [27] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28]. The PubMed, Medline, and Embase databases were searched for papers published between January 2000 and July 2013 using the following key words: [“placenta” OR “chorion”] AND [“MSC” OR “mesenchymal”] AND [“stem cell” OR “progenitor cell” OR “stromal cell”]. No language restrictions were applied, but we specified that the species was human. We also searched the Cochrane Library and ClinicalTrials.gov databases for relevant studies or reviews. We set the start date for the search as January 1, 2000, because prior to this the placenta was not recognized as a tissue source for MSCs. The protocol was finalized prior to the requirement for registration on PROSPERO.

**Study Selection**

Two investigators (C.F.H. and H.S.) undertook the initial screen of titles and abstracts. Any disagreement about selection decisions was then discussed, and a consensus was reached between the investigators and the senior authors. Full manuscripts of papers identified as potentially relevant were then sourced and reviewed independently by the same two authors against the three inclusion criteria. Again, any disagreement was discussed, and concordance was reached. Review papers not included in the analysis were scanned for relevant references. Duplicate articles and those published in a language other than English were excluded.

Inclusion criteria comprised firstly original publications using MSCs harvested from (a) the chorion (which in addition to chori- rionic villi and/or chorionic plate retrieved articles on chorion leave and chorion membrane) or (b) the placenta. We did not include studies of MSCs sourced specifically from other adnexal regions (such as amniotic membrane, amniotic fluid, cord blood/umbilical cord/Wharton’s jelly), nor studies of complicated pregnancies (e.g., pre-eclampsia). Next, studies needed to satisfy minimal characterization criteria, comprising both a CD105+ / CD73+/CD45− cell surface phenotype [20] and evidence of at least bilineage mesodermal differentiation into fat, bone, or cartilage. Although acknowledging that a precise definition for MSCs remains elusive, we set these criteria at a relatively basic level to avoid exclusion of studies published in the earlier part of the study window prior to the International Society of Cell Therapy’s criteria for defining multipotent mesenchymal stromal cells set in 2006 [3] and for placental MSC published by the International Placental Society for Stem Cells in 2008 [20]. Finally, to determine maternal contamination/overgrowth in fetal cultures, the included studies had to determine the fetal or maternal origin, either by testing for gender in pregnancies with male fetuses using karyotyping, fluorescence in situ hybridization (FISH), or polymerase chain reaction (PCR) with a male-specific (Y-chromosome) marker, or using PCR for other fetal polymorphic DNA markers as shown in Table 1.

We also undertook a prespecified secondary analysis of those studies documenting cell origin to inform why maternal contamination and/or overgrowth occurs within placental and/or chorionic MSC cultures. Data were extracted on gestational age, tissue sampling site, isolation technique, genotyping method, passage number, sample size, and number of donors and then referenced to MSC origin and purity. Significant associations were sought using Fisher’s exact test.

**RESULTS**

Figure 1 outlines the flow process for inclusion or exclusion of studies. The database search yielded 540 abstracts that matched key-word terms. After excluding review articles (n = 111), studies published in a language other than English (n = 54), conference abstracts (n = 49), and studies that did not refer specifically to MSCs from either placenta or chorion (n = 169), that sourced MSCs from complicated pregnancies (n = 8), or that reported methods protocols only (n = 2), full manuscripts of 147 studies underwent detailed review. Of those 147 studies, 96 were excluded for not satisfying the minimal MSC characterization criteria, and then a further 36 were excluded for not reporting on the origin/gender of the MSCs. Therefore, only 15 of the 147 studies reviewed, meeting the full criteria for inclusion (Table 1). These numbers highlight the paucity of studies that specifically address the issue of cell origin in cultured placental and/or chorionic MSCs.

**Analysis of Cell Origin**

Of the 147 studies purporting to be of placental and/or chorionic MSCs, 102 (69%) investigated placental and/or chorionic MSCs biology, whereas 45 (31%) explored potential therapeutic applications. After excluding studies that did not meet minimal characterization criteria, only 15 (29%) tested the gender from informative pregnancies as an index of cell origin (i.e., were reported as male babies). Table 1 shows 15 informative studies classified into MSC cultures of pure fetal (n = 8) or maternal/mixed origin (n = 8) based on testing for fetal gender or DNA sequences using either PCR, FISH, or karyotyping. One study
reported separately culturing pure maternal and pure fetal MSC from different regions of the same placenta/chorion. Of the studies classified as maternal/mixed origin cultures, only one reported a mixed population of cells. Thus, maternal contamination was equally as frequent as pure fetal populations in placental and/or chorionic MSC cultures.

Determinants of Decidual Contamination

The 15 fully informative studies that satisfied the minimal MSCs characterization criteria underwent secondary analysis as shown in Table 1 separated into fetal versus maternal/mixed groups.

Sampling Site

Within the 15 studies, two distinct tissue-sampling sites were discerned: the placenta (chorionic villi) and the chorionic membrane. None of the eight studies reporting MSCs of fetal origin sourced them from the chorionic membrane. In contrast, five of the eight studies reporting maternal- or mixed-origin-derived cells sourced them from the chorionic membrane (p < .05). Thus, all five studies of chorionic membrane MSCs showed maternal contamination. This is perhaps not surprising in that the fetal chorionic membrane is intimately related to and often difficult to separate from the underlying decidual, as indicated by use of the term chorioidecidua to describe the apposed two structures. However, there were still three studies reporting maternal contamination that sampled cells exclusively from areas of the placenta considered purely fetal in origin, i.e., chorionic villi from the placental mass. Wang et al. [35] separately grew pure fetal and maternal MSC cultures by harvesting 1.0- and 0.5-cm pieces, respectively, from opposing sides of the same placenta (i.e., the chorionic plate for fetal and the basal plate for maternal MSCs).

Gestational Age

None of the studies that included first trimester MSCs reported maternal contamination, whereas this was present in 8 of 13 studies (61%) that isolated chorionic MSCs populations at term. However, there were only three informative studies of first-trimester MSCs, so this did not attain statistical significance. No first-trimester study used chorionic membrane, so it was not possible to exclude sampling site as a confounder. There were no informative studies that tested the origin of cells harvested from second-trimester placentas.

Isolation Method

The cell isolation methods reported for harvesting placental MSCs were either mechanical and enzymatic digestion and explant culture. Most studies used mechanical and enzymatic digestion, including all eight reporting maternal contamination.

Cell Origin Testing

The techniques used in the 15 studies to establish maternal contamination/overgrowth relied in most cases (n = 13) on testing for gender in pregnancies with male fetuses and included karyotyping, PCR, FISH, or a combination of these. The remaining two studies tested irrespective of fetal gender using PCR for an autosomal variable number tandem repeat to test samples for maternal and fetal alleles documented in cord and maternal blood samples [40] and polymorphic tandem repeat loci [35]. Two studies quantitated cell purity by counting the number of cells that expressed XY and/or XX signals using FISH [21, 30], both reporting pure fetal in origin. A mean of 95 cells expressing XY signals from 7 donors was reported by Igura et al. [30], whereas a total of 100 cells per group were analyzed from 5 donors by Jones et al. [21].

Table 1. Study details of secondary analysis of determinants of fetal versus maternal origin mesenchymal stem/stromal cell

| Study Details | Gestational age | Tissue sampling site | Isolation technique | Origin testing technique |
|---------------|----------------|----------------------|---------------------|-------------------------|
| Fetal         |                |                      |                     |                         |
| Chen et al. [29] | Term          |                      |                     |                         |
| Igura et al. [30] |                |                      |                     |                         |
| Jones et al. [21] |                |                      |                     |                         |
| Li et al. [31] |                |                      |                     |                         |
| Nazarov et al. [32] |                |                      |                     |                         |
| Poloni et al. [33] |                |                      |                     |                         |
| Poloni et al. [34] |                |                      |                     |                         |
| Wang et al. [35] |                |                      |                     |                         |
| Maternal      |                |                      |                     |                         |
| Barlow et al. [36] |                |                      |                     |                         |
| Castrechini et al. [17] | Term       |                      |                     |                         |
| Jaramillo-Ferrada et al. [37] |                |                      |                     |                         |
| Macias et al. [16] |                |                      |                     |                         |
| Ringdén et al. [38] |                |                      |                     |                         |
| Semenov et al. [39] |                |                      |                     |                         |
| Soncini et al. [40] |                |                      |                     |                         |
| Wang et al. [35] |                |                      |                     |                         |

Abbreviations: FISH, fluorescence in situ hybridization; PCR, polymerase chain reaction; SRY, sex determining region Y.
Passage Number
Overall analysis by passage number was precluded by the number of papers not reporting this variable ($n = 5$), and the broad range in those that did (i.e., P3–P8).

**DISCUSSION**

Although current standards in MSC isolation insist on characterization of the fetal or maternal origin of MSCs [20], the lack of consistency that we document in application of this over the last decade may confound reports of efficacy or clinical advantage of fetal MSCs. Although the commercial cord blood banking industry advertises the properties of cord blood MSCs, these cells are reliably obtainable in only around half of cases, at best. The far greater reliability and yield of MSCs from abundant chorionic tissue in the human placenta makes this a more attractive source of MSCs and is the predominant perinatal source in current clinical trials.

Our systematic review highlights the potential difficulties in obtaining pure fetal MSCs from placental chorion cultures, because a comparable proportion of chorionic MSC cultures instead proved maternal or mixed in origin. The main and only statistically significant association as a likely contributing factor to maternal cell contamination was the sampling site (i.e., chorionic membrane versus chorionic villi). The close physical proximity between the fetal-derived chorion (chorionic membrane, chorionic plate, and chorionic villi) with the maternal decidua may account for studies that sampled the chorionic membrane reporting a maternal MSC population. Thus, the association of maternal cell contamination with chorionic membrane-derived MSCs documented in our secondary analysis is not unexpected, because others have actually derived decidual MSCs from this source [17, 41, 42]. Here the fetal chorionic membrane adheres to the underlying and partially adherent maternal decidua parietalis and as such has been termed choriodecidua. Indeed, all chorionic membrane-derived MSC samples showed maternal contamination.

Notwithstanding this, we still found maternal cell contamination in 30% of samples sourced from chorionic villi, in each of which the sample proved entirely maternal by passage 3. Indeed Wang et al. [35] separately obtained pure fetal and maternal MSC cultures from the opposing fetal and maternal sides of the same placenta. This may seem the obvious experiment, but their paper did not specify sample numbers or quantitate purity. Our own recent experience is that maternal origin cultures may be still readily obtainable from samples sourced from near the chorionic plate.

Passage number is likely to be another important determinant. Soncini et al. [40] in chorionic membrane MSCs used tandem repeats to report that maternal alleles that were absent in fresh samples then increased in frequency over two or three passages. This is in contrast to Wang et al. [35] who did not observe such increases. Indeed, our own experience is that the rate of maternal allele increases is not consistent among placenta. We therefore propose that other factors such as passage number and time to freezing are important in the rate at which maternal cell contamination occurs.

**Figure 1.** Work flow and inclusion criteria. Abbreviation: MSCs, mesenchymal stem/stromal cells.
passages, reflecting mixed maternal and fetal cell populations but not complete maternal overgrowth. A further study [43], which did not meet our MSC characterization criteria and thus is not shown in Table 1, similarly reported a mixed population of fetal and maternal MSCs up to P2 in culture, with complete overgrowth of maternal cells thereafter. Together, these two studies suggest that maternal contamination (likely from decidua) outgrows fetal MSCs at around P3. This is supported by three other studies, reporting maternal-only cells in term placental and/or chorionic MSCs cultures at passage 3 at the earliest [36, 37, 39], although in the absence of quantitative data, these studies did not show that cultures were entirely of maternal cells. In contrast, however, Jones et al. [21] tested chorionic villi MSCs between P3 and P9 using FISH and reverse transcription-PCR (SRY) to show cells of fetal origin with no maternal contamination, both at term and in the first trimester.

Competitive outgrowth of fetal by maternal cells may be explained by the increased proliferative capacity of maternal decidual MSCs. Although fetal MSCs are widely reported to have superior growth characteristics and longevity in culture compared with adult MSCs, direct comparison of maternal versus fetal MSCs in placental cultures shows a different story. Maternal MSCs proliferate faster than fetal MSCs in selected culture media, which may reflect the proliferative and regenerative abilities of the endometrial niche [36, 44] and the fact that decidua is a pregnancy specific and thus a “young” tissue. One group commercializing maternal origin placental MSC as a therapy [24] has managed to separate pure maternal from mixed or fetal cell populations to report superior neural repair but less anti-inflammatory activity with maternal source cells [26], but these papers did not satisfy the minimal characterization requirements for inclusion in our systematic review [25].

In addition, it is salient to note that studies reporting continued fetal MSCs growth over a large number of passages, (in some cases >20 passages) have predominantly used somatic fetal tissues from early trimester embryos [5, 6, 8] rather than placental and/or chorionic tissues as addressed in this systematic review. However, ontological age as compared with source may also be of relevance, because there was no report of maternal cell contamination in first trimester placenta, although admittedly this was limited by the inclusion of only three studies from early pregnancy, and maternal cell contamination is a known issue in long-term cytogenetic cultures of chorionic villi.

The presence of maternal cells might also be explained by contamination with maternal blood during the isolation process, although circulating MSCs in adult blood are exceedingly rare and thus difficult to culture with standard methods [45, 46]. Another unlikely possibility is active invasion of microchimeric maternal cells into the chorion during pregnancy [40]. Fetomaternal microchimerism is a well-recognized phenomenon with fetal cells found at remote maternal organs [47], and increasing evidence points to a bidirectional cellular exchange between the mother and fetus, resulting also in maternal cells engrafting in fetal organs [48]. However, this is a rare event phenomenon, typically seen only as single cells, rendering complete maternal overgrowth within a few passages implausible.

Gender dimorphism is increasingly recognized in placental studies [49, 50], and we acknowledge this as a possible bias in our findings, because all but one included study used tissues from male progeny to document cell origin. Adult female MSCs sourced from mouse bone marrow are known to produce more growth factors when stressed compared with similarly isolated male MSCs [51], although it is not known whether human fetoplacental MSCs are similarly dimorphic. A further potential source of bias might be the MSC criteria we applied before selecting studies reporting cell origin. However, when we filtered first by cell origin, the proportion of studies of maternal/mixed origin (12 of 26, 46%) was still high. We acknowledge that cell origin testing was often not based on large denominators, and as such, such low level chimerism could not be excluded.

**Conclusions**

This systematic review emphasizes the importance of testing the origin of placental chorionic MSC populations, because maternal contamination is a genuine and frequent concern. Because the use of placental MSCs has become increasingly translational with clinical trials under way, it is imperative that the high chance of maternal cell contamination and maternal overgrowth in long-term culture is acknowledged. Commencing clinical trials and cryobanking cells for future translation without ascertaining the genetic donor (mother or fetus) seems premature. Our report should encourage attempts to isolate separate haploidentical MSC populations from the fetal and maternal origin portions of the same placenta, which may prove an important advantage for their future use in autologous and allogeneic transplantation. Future studies should also focus on the comparative biology of fetal-placental versus maternal MSCs to determine conclusively their relative functional and mechanistic properties. Although it is widely assumed that fetal origin cells are translationally advantageous, we acknowledge, at least in the absence to date of such comparison, that decidual MSCs might be preferable for certain clinical indications or for cases in which the mother rather than the child requires treatment from an autologous placental MSC bank.

We recommend that investigators using placental chorionic MSCs test their origin on ex vivo expanded cells prior to experimental use to establish robust methodology in isolating and characterizing the resultant MSCs populations. Cell origin testing as a quality control measure should occur repeatedly and in combination, using multiple tests that can sensitively establish maternal contamination in a “bulk” population of cells (rather than a small subsample). Karyotyping is informative only with male fetuses but has the additional benefit of determining the safety and genetic stability of the cell population. The following guidelines for testing cell origin will reinforce the importance of establishing robust methodology and standardization in the placental MSCs field, because it is important for investigators to compare and reproduce results that lead to improved understanding of MSCs’ mechanistic abilities. Our findings similarly have significant implications for placental MSC banking.

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REFERENCES

1 Millard SM, Fisk NM. Mesenchymal stem cells for systemic therapy: Shotgun approach or magic bullets? BioEssays 2013;35:173–182.

2 Pittenger MF, Mackay AM, Beck SC et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–147.

3 Dominici M, Le Blanc K, Mueller J et al. Minimal criteria for defining multipotent mesenchymal stem stromal cells: The International Society for Cellular Therapy position statement. Cytotherapy 2006;8:315–317.

4 Troeger C, Perahud I, Moser S et al. Transplacental traffic after in utero mesenchymal stem cell transplantation. Stem Cells Dev 2010;19:1385–1392.

5 Campagnoli C, Roberts IA, Kumar S et al. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal liver, blood, and bone marrow. Blood 2001;98:2396–2402.

6 Götherström C, Rindgön O, Westgren M et al. Immunomodulatory effects of human foetal liver-derived mesenchymal stem cells. Bone Marrow Transplant 2003;32:265–272.

7 Roelen DL, van der Mast BJ, Int’Akker PS et al. Differential immunomodulatory effects of fetal versus maternal multipotent stromal cells. Hum Immunol 2009;70:16–23.

8 Guillot PV, Gotherstrom C, Chan J et al. Human first-trimester fetal MSC express pluripotency markers and grow faster and have longer telomeres than adult MSC. Stem Cells 2007;25:646–654.

9 Chan J, O’Donoghue K, Gavina M et al. Galectin-1 induces skeletal muscle differentiation in human fetal mesenchymal stem cells and increases muscle regeneration. Stem Cells 2006;24:1879–1891.

10 Dan YY, Riehle KJ, Lazarow C et al. Isolation of multipotent progenitor cells from human fetal liver capable of differentiating into liver and mesenchymal lineages. Proc Natl Acad Sci USA 2006;103:9912–9917.

11 Kennea NL, Waddington SN, Chan J et al. Differentiation of human fetal mesenchymal stem cells into cells with an oligodendrocyte phenotype. Cell Cycle 2009;8:1069–1079.

12 Ramkissoon EA, Pijnappels DA, Askar SF et al. Human embryonic and fetal mesenchymal stem cells differentiate toward three different cardiac lineages in contrast to their adult counterparts. PLoS ONE 2011;6:e24164.

13 Portmann-Lanz CB, Schoberlein A, Huber A et al. Placental mesenchymal stem cells as potential autologous graft for per- and peri-natal neuroregeneration. Am J Obstet Gynecol 2006;194:664–673.

14 Lee HJ, Jung J, Cho KH et al. Comparison of in vitro hepaticogenic differentiation potential between various placenta-derived stem cells and other adult stem cells as an alternative source of functional hepatocytes. Differentiation 2012;84:223–231.

15 Guillot PV, O’Donoghue K, Kurata H et al. Fetal stem cells: Betwixt and between. Semin Reprod Med 2006;24:340–347.

16 Macias MI, Grande J, Moreno A et al. Isolation and characterization of true mesenchymal stem cells derived from human term decidua capable of multilineage differentiation into all 3 embryonic layers. Am J Obstet Gynecol 2010;203:495.e9–495.e23.

17 Castrechini NM, Murtpi H, Qin S et al. Decidua parietalis-derived mesenchymal stromal cells reside in a vascular niche within the choriochorioid. Reprod Sci 2012;19:1302–1314.

18 Nagan N, Faulkner NE, Curtis C et al. Laboratory guidelines for detection, interpretation, and reporting of maternal cell contamination in prenatal analyses a report of the association for molecular pathology. J Mol Diagn 2011;13:7–11.

19 Schrijver I, Cherny SC, Zehnder JL. Testing for maternal cell contamination in prenatal samples: A comprehensive survey of current diagnostic practices in 35 molecular diagnostic laboratories. J Mol Diagn 2007;9:394–400.

20 Parolini O, Alivano F, Bagnara GP et al. Concise review: Isolation and characterization of cells from human term placenta: Outcome of the first international Workshop on Placenta Derived Stem Cells. STEM CELLS 2008;26:300–311.

21 Jones GN, Moschidou D, Puga-Iglesias Ti et al. Ontological differences in first trimester human placenta derived multipotential stem cell. PLoS ONE 2012;7:e43393.

22 Rus Ciucă D, Sorţăţu O, Suşman S et al. Isolation and characterization of chorionic mesenchymal stem cells from the placenta. Rom J Morphol Embryol 2011;52:803–808.

23 Pluristem Therapeutics Inc. Clinical Program. March 2014. Available at http://www.pluristem.com/index.php/clincial-program.html.

24 Prather WR, Toren A, Meiron M. Placental-derived and expanded mesenchymal stromal cells (PLX-K) to enhance the engraftment of hematopoietic stem cells derived from umbilical cord blood. Expert Opin Biol Ther 2008;8:1241–1250.

25 Gaberman E, Pinzur L, Levdansky L et al. Mitigation of lethal radiation syndrome in mice by intramuscular injection of 3D cultured adherent human placental stromal cells. PLoS ONE 2013;8:e60549.

26 Kranz A, Wagner DC, Kamprad M et al. Transplantation of placenta-derived mesenchymal stromal cells upon experimental stroke in rats. Brain Res 2010;1315:128–136.

27 Systematic Reviews: CRD’s Guidance for Undertaking Systematic Reviews in Health Care. York, U.K.: Centre for Reviews & Dissemination, 2009.

28 Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. Phys Ther 2009;89:873–880.

29 Chen CP, Liu SH, Huang JP et al. Engraftment potential of human placenta-derived mesenchymal stem cells after in utero transplantation in rats. Hum Reprod 2009;24:154–165.

30 Isga K, Zhang X, Takahashi K et al. Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. Cytotherapy 2004;6:543–553.

31 Li C, Zhang W, Jiang X et al. Human-placenta-derived mesenchymal stem cells inhibit proliferation and function of allogeneic immune cells. Cell Tissue Res 2007;330:437–446.

32 Nazarovi I, Lee JW, Soupene E et al. Multipotent stem cell lines from human placenta demonstrate high therapeutic potential. STEM CELLS TRANSLATIONAL MEDICINE 2012;1:359–372.

33 Poloni A, Rosini V, Mondini E et al. Characterization and expansion of mesenchymal progenitor cells from first-trimester chorionic villi of human placenta. Cytotherapy 2008;10:690–697.

34 Poloni A, Maurizi G, Babini L et al. Human mesenchymal stem cells from chorionic villi and amniotic fluid are not susceptible to transfection after extension in vitro expansion. Cell Transplant 2011;20:643–654.

35 Wang L, Yang Y, Zhu Y et al. Characterization of placenta-derived mesenchymal stem cells cultured in autologous human cord blood serum. Mol Med Rep 2012;6:760–766.

36 Barlow S, Brooke G, Chatterjee J et al. Comparison of human placenta- and bone marrow-derived multipotent mesenchymal stem cells. Stem Cells Dev 2008;17:1095–1107.

37 Jaramillo-Ferrada PA, Wolvegent EJ, Cooper-White JJ. Differential mesenchymal potential and expression of stem cell-fate modulators in mesenchymal stromal cells from human-term placenta and bone marrow. J Cell Physiol 2012;227:3234–3242.

38 Ringdön O, Ekers T, Nava S et al. Fetal membrane cells for treatment of steroid-refractory acute graft-versus-host disease. Stem Cells 2013;31:592–601.

39 Semenov OV et al. Multipotent mesenchymal stem cells from human placenta: Critical parameters for isolation and maintenance of stemness after isolation. Am J Obstet Gynecol 2010;202:193.e1–193.e13.

40 Sancin M, Vertua E, Gibelli L et al. Isolation and characterization of mesenchymal cells from human fetal membranes. J Tissue Eng Regen Med 2007;1:296–305.

41 Int’Akker PS, Scherjon SA, Kleijburg-van der Keur C et al. Isolation and characterization of placenta-derived mesenchymal stem cells of fetal or maternal origin from human placenta. STEM CELLS 2004;22:1338–1345.

AUTHOR CONTRIBUTIONS

C.F.H. and H.S.: conception and design, collection and/or assembly of data, data analysis and interpretation, manuscript writing. J.R.: assistance with review criteria and inclusion/exclusion schema; K.A.: data analysis and interpretation, manuscript editing. N.M.F.: conception and design, data analysis and interpretation, manuscript writing.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

K.A. has uncompensated stock options with Mesoblast PTL.
42 Strakova Z, Livak M, Krezalek M et al. Multipotent properties of myofibroblast cells derived from human placenta. Cell Tissue Res 2008;332:479–488.
43 Wulf GG, Viereck V, Hemmerlein B et al. Mesengenic progenitor cells derived from human placenta. Tissue Eng 2004;10:1136–1147.
44 Indumathi S, Harikrishnan R, Mishra R et al. Comparison of feto-maternal organ-derived stem cells in facets of immunophenotype, proliferation and differentiation. Tissue Cell 2013;45:434–442.
45 O’Donoghue K, Choolani M, Chan J et al. Identification of fetal mesenchymal stem cells in maternal blood: Implications for non-invasive prenatal diagnosis. Mol Hum Reprod 2003;9:497–502.
46 Zvaifler NJ, Marinova-Mutafchieva L, Adams G et al. Mesenchymal precursor cells in the blood of normal individuals. Arthritis Res 2000;2:477–488.
47 Seppanen E, Fisk NM, Khosrotehrani K. Pregnancy-acquired fetal progenitor cells. J Reprod Immunol 2013;97:27–35.
48 Chen CP, Lee MY, Huang JP et al. Trafficking of multipotent mesenchymal stromal cells from maternal circulation through the placenta involves vascular endothelial growth factor receptor-1 and integrins. STEM CELLS 2008;26:550–561.
49 Cvitic S, Longtine MS, Hackl H et al. The human placental sexome differs between trophoblast epithelium and villous vessel endothelium. PLoS ONE 2013;8:e79233.
50 Clifton VL. Review: Sex and the human placenta: Mediating differential strategies of fetal growth and survival. Placenta 2010;31(suppl):S33–S39.
51 Crisostomo PR, Markel TA, Wang M et al. In the adult mesenchymal stem cell population, source gender is a biologically relevant aspect of protective power. Surgery 2007;142:215–221.