Review

Ageing in human parturition: impetus of the gestation clock in the decidua†

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Abstract

Despite sharing many common features, the relationship between ageing and parturition remains poorly understood. The decidua is a specialized lining of endometrial tissue, which develops in preparation for pregnancy. The structure and location of the decidua support its role as the physical scaffold for the growing embryo and placenta, and thus, it is vital to sustain pregnancy. Approaching term, the physical support properties of the decidua are naturally weakened to permit parturition. In this review, we hypothesize that the natural weakening of decidual tissue at parturition is promoted by the ageing process.

Studies of the ageing-related functional and molecular changes in the decidua at parturition are reviewed and classified using hallmarks of ageing as the framework. The potential roles of decidual mesenchymal stem/stromal cell (DMSC) ageing in labor are also discussed because, although stem cell exhaustion is also a hallmark of ageing, its role in labor is not completely understood. In addition, the potential roles of extracellular vesicles secreted by DMSCs in labor, and their parturition-related miRNAs, are reviewed to gain further insight into this research area.

In summary, the literature supports the notion that the decidua ages as the pregnancy progresses, and this may facilitate parturition, suggesting that ageing is the probable impetus of the gestational clocks in the decidua. This conceptual framework was developed to provide a better understanding of the natural ageing process of the decidua during parturition as well as to encourage future studies of the importance of healthy ageing for optimal pregnancy outcomes.

Summary Sentence

The decidua ages as the pregnancy progresses, and this may promote and/or facilitate parturition. Ageing is likely the impetus of the gestational clocks in the decidua.
Introduction

During the secretory phase of each menstrual cycle, the maternal endometrium develops a specialized lining of tissue, called the decidua, which is an important requirement for preparing, establishing, and maintaining the pregnancy [1]. The main roles of the decidua are to facilitate proper embryo reception (i.e., recognition, selection, and acceptance), to develop immune tolerance to protect the allogeneic embryo from possible attacks by the maternal immune cells, and to provide a physical scaffold as well as nutrients for the developing embryo prior to the development of the mature placenta [1, 2].

Recent studies reveal the decidua progressively ages as pregnancy approaches term parturition [3], while premature and accelerated ageing of the decidua is associated with preterm parturition [4, 3]. Furthermore, ageing of the decidua may play an essential role in the initiation of labor and thereby be involved in determining the timing of parturition [6, 7]. Nevertheless, the current evidence that ageing, particularly of the decidua, is beneficial or even essential for natural parturition at term is limited. Thus, there are ample opportunities for further investigation. Here, we review current findings and knowledge of the association between ageing, timing of parturition, and the decidua. Furthermore, the possible roles of important resident cells of the decidua, particularly mesenchymal stem/stromal cells (MSCs) and their secreted extracellular vesicles, will be reviewed in the framework of an “ageing–decidua–parturition axis.” Finally, we review the general advantages and disadvantages of models for studying the “ageing–decidua–parturition axis.”

The multiple features of ageing: the impetus of the clock of life

Ageing initiates, drives, and ultimately terminates a person’s life by exerting different effects at various development stages (Figure 1). While the detrimental effects of advanced adult ageing (e.g., loss
of vigor, increased morbidity and mortality risks) are well-known [8], recent evidence supports that ageing may play beneficial roles in early human development by facilitating pregnancy and parturition [9, 10]. For example, at the early stages of gestation, ageing of the syncytiotrophoblast layer of the chorionic villi maintains normal placental development and function, which is required to sustain pregnancy [9]. At later stages of gestation, the ageing of various gestational tissues, e.g., the fetal membranes [11, 12] and decidua [3, 4], may weaken physical supports for the fetus [12] and promote the secretion of various cellular signaling molecules (e.g., pro-inflammatory cytokines) required for labor and parturition [3, 13]. After birth, the features of ageing accumulate over time and intensify post-adulthood because the dysfunctional burden of accumulated aged cells/tissues outpaces the rejuvenation capacity of stem cells. The stem cell population itself undergoes age-related exhaustion (i.e., decrease in cell number and function) [14, 15]. This concept of stem cell exhaustion may also apply when ageing occurs to promote parturition in healthy term pregnancies, yet this area has not been fully investigated. In contrast to the extensive studies performed on the detrimental effects of ageing associated with advanced age, the beneficial effects of ageing at the early stages of life, particularly in association with parturition, are rarely explored despite displaying many common features.

**Timing of parturition: the key to pregnancy success and perinatal outcome**

Human parturition normally occurs between 37 and 42 weeks of gestation, the period that is commonly called “term.” The American College of Obstetricians and Gynecologists Committee [16] redefined “term” parturition into several specified periods, i.e., early-term (37 weeks 0 days to 38 weeks 6 days), full-term (39 weeks 0 days to 40 weeks 6 days), late-term (41st week), and post-term (42 weeks and beyond). The redefinition of “term” parturition was necessary to address differences in the risk of adverse perinatal outcomes throughout the “term” period, with a higher risk observed in early- and late-/post-term [17, 18].

The timing of parturition varies between species and among individuals within the same species. The discrepancy between species indicates differences in the time to accommodate complete fetal growth before birth. Discrepancies within the same species (e.g., pre-, early-, full-, late-, and post-term period in humans) indicate the existence of more than one regulatory mechanism, widely known as “gestational clocks,” which determine the endpoint of human pregnancy. The gestational clocks work in diverse and redundant manners to compensate for the possibility that one or more regulatory pathway(s) may fail to occur at the appropriate time (as reviewed in [10, 19]).

Various types of gestational clocks are proposed and are further classified based on the tissue compartments (i.e., fetal membrane, decidual, myometrial, placental, and fetal clocks) or the molecular pathways involved (i.e., endocrine, immune, proteomic, and epigenetic clocks) (Figure 2). In brief, the fetal membrane clock refers to the initiation of parturition by fetal membrane senescence [12]. The decidual clock signifies the initiation of parturition by the upregulation of inflammatory signals secreted by the decidua [13]. The myometrial clock refers to the initiation of parturition by increased inflammatory load on the gravid myometrium leading to progesterone withdrawal [10]. The placental and fetal clocks signify an increase in corticotrophin releasing hormone (CRH) secretion by placental trophoblasts [20] and an upregulation of the fetal hypothalamic pituitary adrenal (HPA) axis to stimulate various hormonal cascades required for the maturation of fetal organs (e.g., lungs) [21] as pregnancy approaches term. The endocrine clock refers to the roles of fetal and placental hormones, e.g., CRH and HPA axis during the onset of labor [10]. The immune clock is based on the chronology of immune cell behaviors in peripheral blood, their interconnected pathways and changes as pregnancy progresses [22]. The proteomic clock refers to the dynamic changes of the plasma proteome during pregnancy [23]. The epigenetic clock is based on the regulation of DNA methylation in association with labor [24, 25].

Despite abundant evidence of various gestational clocks, the mechanisms by which these gestational clocks sequentially or simultaneously work to initiate parturition remain unclear. In this review, we propose ageing as the driving force behind the gestational clocks because many hallmarks of ageing are present in various gestational tissues during parturition and aberrant ageing of the gestation tissues, e.g., the placenta, fetal membranes, and decidua are strongly associated with preterm parturition (as reviewed in [9]).

**Building the link between parturition and ageing**

Ageing and parturition share common features. Firstly, increased sterile inflammatory responses are evident in both cases. The onset of labor involves the release of the endogenous sterile
inflammatory stimuli (e.g., the nuclear protein high mobility group box 1 (HMGB1) [26] and cell-free fetal DNA [27]) by various gestational tissues. These stimuli activate toll like receptor (TLR) pathways, which in turn trigger nuclear factor NFκB to increase the transcription of many genes, particularly those encoding the inflammatory cytokines [28, 29], such as interleukin (IL) 1β, IL6, IL8, IL10, granulocyte macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-alpha [30, 31]. A significant increase of IL1B, IL6, and IL8 is observed in the cervix and myometrium, interferon gamma (IFNG), IL6 and IL8 in the chorio-decidua, as well as IL1B and IL8 in the amnion during labor at term [32, 33]. The elevation of pro-inflammatory cytokines triggers labor by stimulating the production of prostaglandins (PGs) and M10 matrix metallopeptidases (MMPs). Cervical ripening involves the increase of MMP1, MMP3, MMP8, MMP9, cathepsin S, prostaglandin-endoperoxide synthase 2 (PTGS2), and PGE2 [34, 35]. Membrane rupture involves the increase of MMP9, collagenases, and PGs as well as the decrease of TIMP metallopeptidase inhibitor 2 (TIMP2) [34, 35]. Myometrial contractility involves the increase of PTGS2, PGE2, and oxytocin receptor, which stimulates myocyte contraction [34, 35].

In relation to ageing, accumulating evidence shows that chronic and progressive increase of pro-inflammatory factors (inflamm-ageing) [36] is one of the main features of ageing. Inflamm-ageing belongs to the integrative hallmarks of ageing, particularly in the altered intercellular communication category. The aforementioned parturition-associated pro-inflammatory mediators are predominantly members of the senescence-associated secretory phenotype (SASP) [37, 38]. SASP is a group of pro-inflammatory cytokines, chemokine, growth factors, and proteases commonly secreted by senescent cells. Senescent cells are characterized by the permanent growth arrest, morphological changes, the presence of senescence-associated heterochromatin foci (SAHF), resistance to apoptosis, as well as increased nuclear factor NFκB, which, as explained above, contribute to the parturition-related inflammation pathway [39]. Recent studies show that senescent cells accumulate in tissue with increasing age [40, 41]. Senescence is also implicated as a primary cause of age-related diseases [42] since experimental clearance of senescent cells delays the appearance of ageing-related phenotypes and extends the health span of mice (as reviewed in [43]). With regard to inflamm-ageing, the secretion of SASP by senescent cells is proposed to promote chronic inflammation during the ageing process [38, 44]. Based on this understanding of ageing and parturition, it is likely that ageing of various gestational tissues, through cellular senescence, contributes to increased production of pro-inflammatory factors with impending parturition. Nevertheless, further investigation is required to identify the type of aged cells or gestation tissues that contribute to the increase of the pro-inflammatory signaling during parturition. The threshold level of pro-inflammatory mediators required for normal parturition, or their aberrant level associated with major pregnancy disorders, needs to be determined.
Figure 3. Proposed association between ageing and parturition. Approaching parturition, increased exposure to inflammatory stimuli, prolonged exposure to circulating maternal factors, and various physiological events during delivery induce oxidative stress within various gestation tissues. As a result, there is an increase in the production of pro-inflammatory factors and the number of senescent cells, and a decrease in the number and function of stem cells within the tissue. These factors work in a cycle-like mechanism with a similar outcome, which is the weakening of physical support (clinically referred as labor).

Another common feature shared by ageing and parturition is the weakening of physical support. In parturition, this occurs during labor and indicates programmed tissue disintegration by the resident cells to promote the delivery of the fetus. In many studies, most notably those of muscle tissues, the loss of tissue integrity/strength is associated with stem cell exhaustion during the ageing process [45–47]. It is likely that as pregnancy approaches term, stem cell exhaustion is naturally scheduled to reduce gestation tissue integrity and allow parturition. There are various possible causes of gestation tissue-derived stem cell exhaustion. Recent evidence shows that inflammation, through the prolonged secretion of SASP, may impair normal stem cell function and behavior, and thus hamper tissue repair and regeneration in aged organisms [48–50]. As parturition is strongly related to inflammatory pathways [51], these findings provide indirect support for inflammation as the possible cause. Nonetheless, additional studies are required to confirm whether the exposure period and level of pro-inflammatory mediators circulated during pregnancy affect stem cell function leading to labor.

In addition to inflammation, stem cell exhaustion also results from DNA damage and/or increased exposure to reactive oxygen species (ROS) [52]. Similarly, increased exposure to ROS is a feature of term pregnancy. Laboring gestational tissues are constantly exposed to high oxidative stress due to increased pro-inflammatory stimuli and prolonged exposure to circulating maternal factors. During delivery, various physiological changes in the uterine environment further elevate ROS production. These changes include alternating ischemia and reperfusion due to suppressed uteroplacental blood flow, a rapid transition from hypoxic intrauterine to oxygen-rich extraterine environment, and higher oxygen consumption resulting in increased mitochondrial respiration [11, 53]. Higher lipid peroxidation and protein oxidation as well as lower expression of antioxidant enzymes are also detected in labor-myometrial samples, indicating an increased susceptibility of the laboring myometrium to oxidative damage [54]. With regard to stem cells, it is possible that gestation tissue-derived stem cells are also subjected to the similar oxidative stressors approaching parturition. Nevertheless, additional studies, particularly those that identify the specific type of stem cell function affected, are required to obtain a better understanding of the role of stem cells in labor. The proposed association between ageing and parturition is shown in Figure 3.

Decidual ageing and its potential role in parturition

The decidua is crucial for the implantation of the blastocyst, supporting the early embryo, as well as anchoring and maintaining the developing placenta, and because of these important roles, the decidua remains the subject of intense research [1, 55]. In contrast, much less is known about the role of the decidua in the late stages of pregnancy, particularly during parturition where the physical support properties of the decidua may be weakened because of the ageing process. In this section, the general feature of decidual ageing and its potential role in parturition will be discussed in relation to the hallmarks of ageing proposed by López-Otín et al. [63]. Most evidence is derived from
animal model studies, which provide insight into possible decidual ageing mechanisms in human. However, animal models of human decidua have significant limitations, and where possible, evidence from human studies is presented.

Physical features of decidual ageing

Studies of rabbit placentae by Larsen [56] and Samuel et al. [57] reported the physical phenotypes of decidual ageing. As gestational age progresses, the degeneration of decidual tissue (i.e., progressive decline in thickness and strength of attachment to the uterine wall) was observed and was proposed to assist the placental expulsion stage of labor [56, 57]. Ultrastructural observation revealed that at parturition, the degenerated DSCs and their fibrous debris accumulated at the “zone of separation” and consequently reduced cell-to-cell interactions between the endometrium and placenta [56]. These deteriorating phenotypes occur to various degrees throughout the decidual tissue at term gestation (28–31 days) and peak at day 31 of gestation when most DSCs begin to undergo fragmentation [57].

Increased tissue degradation at the last stage of gestation was also observed in non-deciduous species. Ultrastructural observation of mare’s uterine glands showed increased numbers of degenerate cells in the secretory epithelium, cellular debris in glandular secretions, and altered size and morphology of the nuclei in the last third of gestation [58]. Together, these data suggest a cellular phenotype for uterine ageing. Unlike decidual species where ageing acts to weaken the strong attachment between the maternal and fetal tissues at parturition, ageing in non-deciduous species may serve an as yet unknown function(s) since the separation of the maternal and fetal tissues of non-deciduous species at parturition involves no uterine tissue damage or bleeding [59]. Erkenbrack et al. [60] reported decidualization signals, which promoted differentiation of endometrial stromal cells into DSCs in humans, induced cellular stress responses (e.g., protection against apoptosis and oxidative stress) in endometrial stromal fibroblasts of the opossum (non-deciduous mammal) [60]. This finding suggests that ageing is a consequence of the stress response during pregnancy in non-deciduous species, but in decidual species it is repurposed to halt decidualization.

Genomic instability in the laboring decidua

While some progress has been made in understanding the role of DNA damage in the decidua in early pregnancy (i.e., decidualization [61]), its role in parturition at the late stage of gestation is poorly understood. A study of rodent decidua suggested an association between decidual tissue degeneration and apoptosis of DSCs, which is characterized by increased nucleosomal DNA fragmentation [62]. Increased DNA damage is strongly associated with ageing [63]. In both the anti-mesometrial and mesometrial regions (which later form the decidua capsularis and decidua basalis, respectively) of the rodent decidua, the degree of DNA fragmentation increased with time, resulting in the apoptosis of DSCs in both tissues [62]. Since the decidua capsularis and decidua basalis are in direct contact with the fetal membranes, and with the maternal side of the placental disk, it is likely that the progressive regression of these regions contributes to the detachment of the fetal membranes and placenta from the uterine wall at parturition.

Epigenetic alterations in the laboring decidua

Reduced DNA methylation associated with increased toll like receptor 2 (TLR2) and toll like receptor 9 (TLR9) gene expression was detected in decidual tissue, specifically in decidual leukocytes (i.e., macrophages and neutrophils), from term not-in-labor, term laboring, and spontaneous preterm birth patients [64]. In general, DNA methylation affects gene expression by regulating gene transcription [65]. Ageing is associated with both hypo- and hypermethylation, which may contribute to functional decline by initiating chromosome instability through heightened gene responsiveness (hypo-methylation), or by highly suppressing gene expression (hypermethylation) [66]. With regard to parturition, the activation of the TLR pathway results in the upregulation of labor-associated proinflammatory cytokines. Decreased DNA methylation of TLR2 and TLR9 is associated with increased expression of the receptor proteins and contributes to increased sensitivity of decidual tissue to inflammatory stimuli and leukocyte infiltration. The decline in DNA methylation of TLR2 and TLR9 observed in term laboring decidual tissues is even greater in spontaneous preterm birth samples [64]. TLR2 and TLR9 may be activated in response to damage-associated molecular patterns (DAMPs) released by senescent fetal membranes at term labor [67, 68]. TLR2 and TLR9 may also be activated by pathogen-associated molecular patterns (PAMPs) as a result of infections during preterm birth [69–71].

The regulation of gene expression by DNA methylation operates concurrently with histone modifications (e.g., histone acetylation and deacetylation, catalyzed by histone acetyltransferase (HAT) and histone deacetylase (HDAC), respectively). Histone acetylation is associated with increased transcriptional activity, whereas deacetylation produces the opposite effect [66]. With regard to parturition, studies of human and murine myometrium report a decline in the expression of progesterone receptor (PR) coactivators containing HAT and the level of histone acetylation at term. Moreover, in a murine model, delayed parturition was observed after administration of a potent histone deacetylase inhibitor, trichostatin A, which increased the level of myometrial histone acetylation [72]. These findings suggest a mechanism that links changes in acetylation with decreased PR expression near term, which reduces tissue responsiveness to progesterone stimuli and leads to increased tissue sensitivity to the contractile stimuli required to initiate labor: a phenomenon called functional progesterone withdrawal. Consistent with this proposed mechanism, a significant decline in PR expression was observed in the decidua at term labor. The decrease in decidual PRs may also result from exposure to PGF2α, which is typically secreted by the laboring decidua at term [73]. Studies of the expression of HAT and histone acetylation are limited to myometrial tissue and have not been carried out in decidual tissue. Nonetheless, this epigenetic mechanism may also apply to the decidua since the same outcome of reduced expression of PRs is detected in both tissues [72, 73]. Whether alterations in histone modification patterns as pregnancy approaches term parturition are caused by the ageing process or not remain to be determined. Establishing the pattern of histone modifications in the ageing decidua is an important prerequisite.

Loss of proteostasis in the laboring decidua

With advancing gestational age, the decidua undergoes changes in its proteostasis, particularly with regard to the expression of heat shock proteins (Hsp). During pregnancy, decreased expression of Hsp90 and Hsp70 was observed in human DSCs [74], whereas at parturition, a study using a ewe model reported elevated levels of Hsp90 and Hsp70 in the laboring decidua, specifically in endometrial gland epithelial cells in both the spontaneous and glucocorticoid-induced labor samples [75]. Increased levels of Hsp70 and Hsp90
are proposed to inhibit the uterine progesterone receptor expression leading to progesterone withdrawal and stimulation of the estrogen receptor, with consequent initiation of labor [75]. Nevertheless, increased levels of Hsp70 above a certain threshold, which mimics the levels associated with systemic inflammation, oxidative stress, and hepatocellular injury, are associated with pregnancy complications, including preclampsia (PE) [76].

Recent studies of the interaction between Hsp70 and autophagy showed autophagy was inhibited by Hsp70 induction (as reviewed in [77]). In contrast to Hsp70, which has a chaperone function to repair and preserve proteins, autophagy works by eliminating defective proteins, organelles, or cells, to maintain proteostasis [77]. With regard to parturition, various findings indicate that decreased autophagy and the associated increased levels of Hsp70 are important for initiating labor. A study by Signorelli et al. [78] showed that autophagy was not detectable in placental sections (i.e., decidual tissue) of patients undergoing spontaneous labor followed by a vaginal delivery but was observed in the placenta of patients who were not in labor and undergoing C-section [78]. Conditional knock out of the crucial autophagy gene Beclin1 (Beclin1) in the luteal cells of the murine ovary inhibited the ability of luteal cells to accumulate lipid droplets required for steroidogenesis, which led to decreased progesterone production, resulting in preterm labor phenotypes [79]. These data imply defective autophagy may promote the onset of labor, and if it occurred prematurely, preterm birth may occur.

The inverse relationship between Hsp70 and autophagy may also involve the activation of the mammalian target of rapamycin complex 1 (mTORC1) signaling pathways. Increased levels of Hsp70 promote the activation of protein kinase B (AKT), which subsequently phosphorylates the mammalian target of rapamycin (mTOR) protein. The phosphorylated mTOR protein combines with an adaptor protein called regulatory associated protein of MTOR complex 1 (RPTOR) to form mTORC1. The mTORC1 complex subsequently inhibits autophagy and promotes phosphorylation and activation of heat shock factor 1 (HSF1). HSF1 attaches to the heat shock protein family A (Hsp70) member 1B (HSPA1B) gene and promotes the production of Hsp70, resulting in the repetition of the cycle (as reviewed in [77]). Labor then becomes the consequence of increased levels of Hsp70 and mTORC1. The association between mTORC1 expression and labor in the decidua will be described in more detail in the following section.

With respect to ageing, Hsp70 is overexpressed when the amount of misfolded protein and its potential cause, ROS, is increased in tissues, which is a typical characteristic of ageing tissue and age-related disease. The overexpression of Hsp70 due to oxidative stress also promotes the secretion of various inflammatory cytokines and receptors, e.g., TNF-alpha, IL1β, IL6, and TLR4, which play roles in initiating labor [80]. Nevertheless, uncontrolled overexpression of Hsp70-mediated inflammatory factors is also strongly associated with pelvic inflammation and endometriosis [81], suggesting the importance of maintaining the level of ageing-related phenotypes only up to a beneficial threshold.

Telomere attrition, cellular senescence, and deregulated nutrient-sensing in the laboring decidua

Bonney et al. [82] showed that telomere length decreased as a function of gestational age in fetal membranes, placenta, and decidua of the murine models [82]. Telomere attrition is regarded as one of the primary hallmarks of ageing and considered to be the common, causative factor of cellular senescence [83]. As term approaches, progressive activation of p38 mitogen-activated protein kinase (MAPK) accompanies the progression of telomere attrition in the decidua, placenta, and fetal membranes [82]. Using the SA-β-Gal assay, Bonney et al. [82] further reported telomere-dependent cellular senescence in the placenta and decidua, however, the extent of cellular senescence was lower than that in the fetal membranes. Since the effect of senescent cells on parturition was strongly associated with their secreted SASPs, Bonney et al. [82] described several potential SASP genes that may be activated in the decidua in relation to ageing or senescence during parturition in the mouse. The potential role of decidual telomere attrition in parturition noted in this study was consistent with previous results in placental samples (as reviewed in [84]). Previous findings in the placenta showed the onset of labor is initiated by the shortening of telomeres, leading to apoptosis of placental trophoblast and chorion cells, subsequent release of fetal cell-free DNA, followed by the induction of oxidative stress, and the innate inflammatory responses (e.g., via TLR9) required for labor (as reviewed in [84]). This mechanism may also apply to the decidua, but this needs to be verified.

With regard to cellular senescence, recent murine studies report a strong correlation between the senescence of DSCs and parturi- tion [3–5, 7]. At term birth, DSCs naturally undergo progressive senescence as parturition approaches, as shown through the gradual increase of SA-β-Gal staining intensity in decidual cells of the term, control murine models from day 16 to 19 (p53+/−) [3]. In preterm birth, this progression of decidual senescence is accelerated, as shown through higher intensity of SA-β-Gal staining in the decidual cells of preterm murine models compared with the term murine models at the same day (day 16, p53+/− versus p53−/−, respectively) [3]. Senescent DSCs may cause parturition through their gradual accumulation within the tissue and their increased secretion of SASPs with gestational age (e.g., MMPs and various pro-inflammatory cytokines) [6]. In parturition, the uterine Trp53 deletion causes the upregulation of mTORC1 signaling, which leads to premature DSC senescence that is characterized by increased decidual expression of AKT and cyclin dependent kinase inhibitor 1A (CDKN1A/p21) [3]. This pathway results in an increased incidence of preterm birth in p53−/− mice [3, 4]. The upregulation of the mTORC1 signaling pathway in this murine model is consistent with parturition-related pathways of Hsp70 and mTORC1 described in the previous section.

With respect to ageing, AKT and p21 are common factors involved in senescence. Early activation/upregulation of AKT and p21 leads to premature senescence by increasing cellular exposure and vulnerability towards oxidative stress [85] and by inhibiting progression of the cell cycle [86], respectively. On the other hand, the mTORC1 protein complex is a sensor for nutrient/redox/energy-sensor pathways, particularly in the detection of a high concentration of amino acids [63]. Studies show the upregulation of mTORC1 signaling promotes premature ageing, and its inhibition (e.g., through calorie restriction) has an antiaging effect (i.e., increased lifespan) [87, 88].

In murine models, inhibition of mTORC1 signaling by rapamycin normalized the progression of DSC senescence and, consequently, averted preterm birth, with only few adverse effects on fetal viability (shown for rapamycin treatment at a dose of 0.25 mg/kg body weight of mice) [5]. Thus, the dysregulation of mTORC1 pathways that leads to preterm birth shows similarities with the pathways associated with premature ageing. Furthermore, the timing of parturition may be determined by the interaction of p53 with its transcriptional target, sestrin2 (SESN2). In murine studies, the interaction between p53 and SESN2 activated 5′ adenosine monophosphate-activated protein kinase (AMPK) signaling, which
subsequently reduced mTORC1 signaling and prevented preterm birth [7]. These findings are consistent with human studies [5, 7].

Unfortunately, investigations of senescence-associated parturition pathways mainly focus on preterm birth [3–5, 7]. The molecular pathways associated with decidual senescence leading to natural term birth, for the most part, can only be inferred. Given that both term and preterm decidual cells exhibited senescence, but to different degrees when observed at the same day [3], the postulate is that term parturition involves the same pathways that promote DSC senescence in preterm birth. However, the regulation of these pathways is different to those in preterm birth. For example, the timing of p53 activation and inhibition as well as the expression level or increasing rate of mTORC1 will differ to ensure the normal pace of decidual senescence ensues for term parturition to occur. Clearly, the regulatory pathways that promote DSC senescence in term parturition and preterm birth need to be elucidated.

Mitochondrial dysfunction and oxidative stress in the laboring decidua

In parturition, the upregulation of SESN2 and AMPK, which leads to the downregulation of mTORC1, delays the timing of parturition (as explained in the previous section). In ageing, the same regulation generates antiaging effects in mammals. SESN is induced through various mechanisms, e.g., p53, nuclear factor, erythroid 2 like 2 (NFE2L2), and JNK-AP-1 signaling axis by oxidative stress, which increases with age. Together with other sestrins (SESN1 and SESN3), SESN2 reduces the accumulation of ROS and stimulates antioxidant responses, e.g., the upregulation of mitochondrial biogenesis and mitophagy (autophagy of abnormal mitochondria) by activating AMPK and inhibiting the mTROC1 signaling pathway. This antioxidant regulatory pathway of sestrin plays an essential role in maintaining metabolic homeostasis and preventing age-related physiological deviations [89]. Nevertheless, the converse of these findings, where decreased SESN2 and increased mTORC1 signaling occur in DSCs, promotes labor by increasing oxidative stress through the downregulation of mitochondrial biogenesis and mitophagy, requires verification.

Pregnancy and parturition are processes associated with high oxidative damage in both maternal and neonatal tissues [53, 54]. With regard to the decidua, a recent study of endometrial stromal cells in the opossum and in humans showed that decidualization in humans, and eutherian mammals in general, evolved from cellular stress responses to oxidative damage, which are a component of pregnancy-related signals [60]. As pregnancy approaches term, pro-inflammatory factors, which exist in the decidua at the later stages of pregnancy, are potent stimulators of ROS production. ROS, subsequently, recruit more pro-inflammatory factors required for labor, and the cycle repeats [53].

Indirect evidence for a role of ROS in promoting term parturition in the decidua was provided in a recent study that compared the level of superoxide dismutase (SOD), lipid peroxide (LPO), and PGF2α in human decidual tissue from spontaneous abortion, and from early stages of uncomplicated pregnancies. Compared to decidual tissue from normal pregnancies, lower levels of SOD and higher levels of LPO and PGF2α were detected in the decidual samples from spontaneous abortion patients [90]. The accumulation of ROS and their products, e.g., LPO, accelerated the termination of pregnancy by stimulating the synthesis of PGF2α, which is required for myometrial contraction [91]. Based on these findings, it is assumed that in early stages of pregnancy, a high level of SOD is maintained to ensure the metabolism of LPO, which prevents the synthesis of PGF2α and maintains myometrial quiescence to sustain pregnancy [90]. Furthermore, although no studies have measured the level of decidual SOD and LPO approaching the end of pregnancy, we hypothesize that the level of decidual SOD declines and LPO increases to allow PGF2α synthesis for labor at term. In contrast, preterm birth, spontaneous abortion, or stillbirth may result from the accelerated/premature decline of decidual SOD as pregnancy progresses and/or from the extremely low level of decidual SOD from the beginning of pregnancy. Further studies are required to test this hypothesis.

High oxidative stress is detected in both healthy and pathological parturition [92]. This may be caused by the dual nature of oxidative stress where its effect is either beneficial or harmful for the organisms depends on the level of ROS. With regard to ageing and age-related diseases, this dual nature of oxidative stress also occurs in a similar fashion. Consequently, “how high is too high for oxidative stress?” becomes a fundamental question that needs to be investigated in both ageing and parturition studies to better predict the occurrence of various associated disorders.

Altered intercellular communication in the laboring decidua

Ageing and parturition both involve changes in intercellular communication. Some examples of these altered intercellular interactions are chronic pro-inflammatory status, declining immune protection, and induced senescence by the adjacent senescent cells. In ageing studies, inflamm-ageing, immunosenescence, and bystander effects are some terms used to describe these phenomena, respectively. With regard to parturition, a recent study of decidual gene expression in spontaneous term labor reported gene changes related to inflammation signaling pathways. Notably, there was increased expression of pro-inflammatory mediators and steroid receptors and decreased expression of anti-inflammatory mediators in the decidua at the onset of labor. The pro-inflammatory mediators and steroid receptors were IL1B, IL6, IL8, estrogen receptor 1 (ESR1), homeobox A11 (HOXA11), progesterone receptor membrane component 2 (PGRMC2), and prostaglandin E synthase (PTGES). The anti-inflammatory mediators include chemokine C–C motif chemokine ligand 2 and 5 (CCL2 and CCL5), galecin 1 and 3 (LGALS1 and LGALS3), and prostaglandin associated endometrial protein (PAEP) [32, 93].

According to the “decidual clock” hypothesis, sterile inflammatory signals, which are associated with the onset of labor, are also significantly upregulated in the decidua through SASP production of the senescent DSCs. The upregulation of proinflammatory cytokines or SASPs, particularly those that are classified as the cytokines of the elderly (i.e., IL6) through their association with frailty and senescence-related diseases, is one of the main characteristics of inflamm-ageing and immunosenescence (as reviewed in [94]). During labor, inflammatory signals and other types of SASPs (e.g., MMPs) are amplified and distributed from the decidua to other gestation tissues, such as the cervix (i.e., to stimulate its ripening), fetal membranes (i.e., to stimulate their rupture), and myometrium (i.e., to stimulate its contractile state), all of which lead to parturition [13]. Additionally, the factors that stimulate the decidua to undergo senescence and amplify the inflammatory signals are proposed to originate from senescent fetal membranes [10]. The claim is plausible given the proximal location of fetal membrane to the decidua [95] and the ability of senescent cells to induce adjacent cells to undergo...
senescence: the so-called bystander effect [96]. One example of the proposed labor-inducing factors from fetal membranes is cell-free telomere fragments released by senescent fetal membrane amnion cells, which are capable of triggering global oxidative stress leading to labor [11].

**Stem cell exhaustion in the laboring decidua**

To the best of our knowledge, no published studies have investigated the potential role of stem cells, particularly decidual mesenchymal stem/stromal cells (DMSCs), in parturition despite some evidence of their possible involvement. DMSCs are the major stem cell types in the decidua. Like other type of stem cells, DMSCs have the ability to regenerate senescent cells, particularly senescent DSCs. During pregnancy, the regeneration of senescent DSCs is essential to sustain the receptive properties of the decidua towards the growing fetus. This hypothesis is supported by a recent study showing that senescent DSCs undergo immunological clearance mediated by uterine natural killer cells (uNK) to maintain decidual homeostasis in the cycling endometrium [97]. This process is crucial for successful decidualization since endometrial MSCs cannot differentiate into new DSCs in the presence of senescent DSCs [97]. In contrast, the inability of MSCs to differentiate in the presence of senescent DSCs is important for parturition. DSCs must not be rejuvenated to ensure that the physical support of the fetus and the placenta can be weakened during labor. As previously described, the deterioration of tissue physical support due to stem cell exhaustion has been reported in studies using muscle stem cells where their exhaustion was associated with the loss of tissue integrity and strength [45–47].

DMSCs are exposed to high levels of oxidative stress and many inflammatory factors as a result of their close proximity to the maternal blood circulation (i.e., located close to the endothelial cells that line the maternal blood vessels [98]), but they are highly resistant to both these types of stimuli. As discussed earlier, high oxidative stress and pro-inflammatory factors are well-established components of parturition. Moreover, our group showed DMSCs are removed from the lining of the blood vessels as a result of spiral artery remodeling, a process that begins in the first few weeks of pregnancy. The extent of remodeling is from the decidua to the first third of the myometrium [98]. The removal of DMSCs from the blood vessel lining of spiral arteries could contribute to the weakening of the maternal–fetal interface in the zone of separation by reducing the number of DMSCs that could participate in repairing and/or maintaining cells in the zone of separation towards the end of pregnancy. With respect to ageing, the loss of cell numbers or functions of stem cells, termed stem cell exhaustion, is an integrative hallmark of ageing. Based on these observations, we hypothesize that DMSCs undergo ageing and/or removal to accommodate parturition. There is no direct evidence in the literature to support this hypothesis, but our recent study provides evidence that DMSCs isolated from placentae of patients undergoing spontaneous onset of labor (SOL-DMSCs) showed signs of ageing (e.g., reduced proliferation and increased apoptosis) compared with DMSCs from placentae of patients, not in labor, undergoing caesarean section (NIL-DMSCs) [99]. SOL-DMSCs also showed significantly altered lipid profiles compared with NIL-DMSCs [99].

Indirect evidence to support a role for DMSC ageing in parturition comes from studies of other tissue-derived MSCs, which will be discussed in more detail below. To conclude, a summary of the features of decidual ageing and its role in parturition is shown in Table 1 and Figure 4.

**Potential roles of mesenchymal stem/stromal cells and their extracellular vesicles in human parturition**

MSCs are multipotent stem cells with the potential to differentiate into various mesenchymal cell lineages, e.g., adipogenic, osteogenic, and chondrogenic. In the decidua, MSCs give rise to DSCs, since the decidua is mostly composed of stromal cells and DSCs also express mesenchymal cell characteristics [100]. The high abundance of MSCs in various gestational tissues and their role in the formation and function of the placenta suggest an important role for MSCs during pregnancy. However, their role, if any, in parturition remains poorly understood. Currently, most studies of the association between MSCs and pregnancy focus on the decline of MSC functions, properties, and differentiation capacity in pregnancy-related disorders that are associated with placental ageing. For example, Rolfo et al. [101] reported that chorionic villous-derived MSCs (CMSCs) from PE patients have reduced proliferation, increased senescence, and increased levels of various pro-inflammatory cytokines (e.g., TNF-alpha, IL6, IL8), chemotactic factors (e.g., macrophage migration inhibitory factors/MIF) and soluble FMS-like tyrosine kinase-1/sFlt1) compared with CMSCs from normotensive patients [101]. On the maternal side, Mayne et al. [102] reported that PE-affected placenta show signs of premature senescence and ageing, including increased SASP, increased apoptosis, and increased expression of ageing-related biomarkers [102]. Furthermore, Kusuma et al. [103] showed that PE-DMSCs have decreased resistance to oxidative stress.

PE-DMSCs also have different microRNA (miRNA) expression (e.g., miR-16, miR-181a, miR-494) compared with DMSCs, particularly in relation to properties such as immunosuppression, proliferation, and angiogenesis regulation [104]. miRNAs are short noncoding regulatory RNAs consisting of about 22 nucleotides that function in mRNA silencing (by cleaving the target mRNAs) and posttranscriptional regulation of gene expression (by suppressing gene translation) [105]. In MSCs, miRNAs are located within the cells or in the secretory, membrane-derived vesicles known as extracellular vesicles (EVs), which facilitate the regenerative properties of MSCs via paracrine function [106, 107]. In pathological situations such as PE, the secretion of EVs containing aberrant miRNA expression by MSCs may contribute to the pathogenesis of PE [104]. In relation to term parturition, these findings may serve as indirect evidence that MSC functions may be altered at parturition, specifically in the decidua, since the decidua shows strong signs of ageing and senescence at parturition. Labor-associated senescence and ageing in the decidua may alter the properties of DSCs, which subsequently act to facilitate labor, e.g., secreting EVs containing parturition-related miRNAs.

Indirect evidence of the role of MSCs in parturition may also be obtained from studies that compare the metabolic activities and functions of mitochondria of human umbilical cord-derived MSCs (hUC-MSCs) between the stages of term not-in-labor and preterm parturition. A study by Panfoli et al. [108] revealed that hUC-MSC-derived exosomes express functional respiratory complexes I, IV, and V and thus have the capacity to conduct aerobic respiration independent of the mitochondria. However, only MSC-derived exosomes of neonates delivered at term not-in-labor were capable of generating ATP as the result of oxidative phosphorylation activity. hUC-MSC-derived exosomes of preterm neonates did not generate ATP after consuming oxygen. Additionally, Ravera et al. [109] suggested that this metabolic difference may originate from differing intracellular mitochondrial regulation. MSCs of preterm
neonates have more scarcely organized mitochondrial reticulum and low expression of mitochondrial fusion-related proteins compared with MSCs of term not-in-labor neonates and these differences were reported to derive from altered expression of clustered mitochondria homolog (CLUH), a cytosolic mRNA-binding protein that governs intracellular biogenesis and distribution of the mitochondria. In MSCs of preterm neonates, the expression of CLUH increased with gestational age but was maintained at a low level. In MSCs of term not-in-labor neonates, CLUH was also expressed in a similar pattern but at higher level compared with MSCs of preterm neonates. The silencing of CLUH in MSCs of term not-in-labor neonates resulted in mitochondrial distribution and metabolic phenotypes similar to

| Hallmarks of ageing | Brief description in association with ageing process | Potential/observed features on decidual | Potential roles in parturition | Ref. |
|---------------------|------------------------------------------------------|--------------------------------------|-------------------------------|------|
| Primary             | Genomic instability                                  | Increased DNA fragmentation with time leading to apoptosis of DSCs | • Fetal membrane rupture • Placental expulsion | [62] |
|                     | Telomere attrition                                   | Decreased telomere length of DSCs with advancing gestational age, resulting in senescent DSCs | SASP-mediated labor process | [82] |
|                     | Epigenetic alterations                               | Reduced DNA methylation in decidual tissue, leading to increased expression of TLRs near term | Increased sensitivity of decidual tissue to inflammatory stimuli | [64] |
|                     |                                                      | Reduced histone acetylation in decidual tissue, leading to decreased expression of progesterone receptor (PR) near term | Progesterone withdrawal at the onset of labor | [72, 73] |
| Loss of proteostasis |                                                      | Elevated level of Hsp70 near term as the response to high oxidative stress and abundant misfolded protein resulting from the inhibition of autophagy through mTORC1 signaling pathway and by-products of senescent DSCs | Progesterone withdrawal and estrogen receptor function stimulation at the onset of labor | [75, 77] |
| Antagonistic         | Deregulated nutrient-sensing                         | Increased mTORC1 signaling pathways (participates in high concentration of amino acid-sensing), leading to natural DSC senescence | SASP-mediated labor process | [3, 7] |
|                     | Cellular senescence                                  | Increased number of senescent DSC (in normal pace) | SASP-mediated labor process | [3, 5, 6] |
|                     | Mitochondrial dysfunction                            | High oxidative stress reflected through increased ROS production and decreased level of antioxidants | • Further recruitment of labor-associated pro-inflammatory factors • Increased PGF2α synthesis required for myometrial contraction | [53, 90, 91] |
| Integrative          | Altered intercellular communication                  | Upregulation of various pro-inflammatory signals (SASPs) released by the senescent DSCs probably is induced by “bystander effect” of the adjacent senescent fetal membrane cells | SASP-mediated labor process | [10, 13] |
|                     | Stem cell exhaustion                                 | Decreased number and function of DMSCs, resulted in the failure to regenerate aged/senescent DSCs | SASP-mediated labor process | [99] |
those of preterm neonate MSCs. The resulting metabolic switch was detected from around the 34th week of gestational age [109].

These findings suggest that there is a metabolic switch in MSCs during gestation, indicating their possible role in promoting labor. The inference is that increased expression of CLUH leads to increased numbers of regularly organized mitochondria, resulting in higher aerobic respiratory activity, which generates ROS as by-products. Consequently, the level of oxidative stress in MSCs, and possibly in their microenvironment, increases. This is consistent with the oxidative stress features of decidual ageing associated with labor, which were described above. In preterm birth, the expression level of CLUH is lower than normal, leading to incomplete aerobic respiration, which may cause higher ROS production than normal. Nevertheless, to investigate the direct association between this metabolic switch and labor, the expression of CLUH on MSCs of term in-labor neonates should be determined.

Potential roles of MSC-derived microRNAs in human parturition. MSCs exert their effects primarily by secreting miRNA-containing EVs (i.e., a paracrine mechanism). With regard to parturition, various miRNAs are associated with the regulation of hormone receptiveness and the main gene expression pathways in parturition (e.g., posttranscriptional regulation of progesterone–progesterone receptor signaling in relation to myometrial contractility during labor) [110]. To see possible associations between miRNAs, MSCs, and parturition, we present a list of miRNAs that are reported to have roles in parturition and their expression in MSCs (Table 2). Although these miRNAs may be expressed in MSCs, in most cases, their potential roles in parturition were inferred by studies of these miRNAs in other types of cells and therefore require confirmation in MSCs. To the best of our knowledge, no studies have investigated the expression of MSC-derived miRNAs in association with parturition.

Potential roles of circadian clock in the laboring decidua and its association with advanced ageing

The roles of circadian clock genes in reproductive success were reported in human studies, where reduced expression (or downregulation) of major circadian transcription factors (e.g., aryl hydrocarbon receptor nuclear translocator like/ARNTL) in human DSCs [111] and clock genes (e.g., period circadian regulator 2/PER2) in the human endometrial stromal cells [112] resulted in impaired decidualization and increased risk of recurrent pregnancy loss. A study employing murine models associated low reproductive success with impaired clock gene (period circadian regulator 1/PER1 and PER2) expression and advanced ageing [113]. The study reported comparable reproductive deficits in middle-aged PER1 and PER2 mutant females (9- to 12-month-old) and aged wild-type mice (13- to 16-month-old). These data suggested a potential role for PER1 and PER2 in the resolution of pregnancy and their mutation in accelerated reproductive ageing [113].

Information of the roles of circadian clock genes in parturition is limited to rodent studies. Reppert et al. [114] reported that maternal suprachiasmatic nuclei (SCN) acted as the central molecular clock in the initiation of parturition. Ratajczak et al. [115] reported persistent expression of circadian clock genes in various parturition-related tissues throughout the last third of gestation. Some of these genes showed about a 2.5-fold increase in expression, while others exhibited rhythmic expression patterns shortly before labor.

The findings above suggested a potential contribution of circadian clock genes in regulating the initiation and progression of parturition through an ageing-related mechanism(s). Given that the decidua and not the fetal labyrinth, exhibited circadian properties (i.e., circadian pattern of PER1 in maternal decidual cells) [116], it is likely that the decidua sends various molecular cues to the fetal cells through the regulation of various circadian clock genes to accommodate parturition at term. Clearly, further investigation is required to identify the specific mechanism of action and the relevance, if any, of these animal model studies to humans.

Studying decidual ageing in human parturition: current and promising study models

Decidual ageing plays a significant role in parturition, and further studies are required to confirm various aspects of this role. However, most studies of decidual ageing in parturition are performed in animal models, e.g., rabbit and rodents [4, 57, 117]. The advantages of using animal models in ageing and parturition studies of decidua are numerous. Since humans are classified as a decidua species, the decidua of human and decidua animals have similar structure (e.g., both human and mice have pre-DSCs that are joined to adjacent cells by gap junctions [118]). Compared with human-based studies,
Table 2. MSC-derived miRNAs and their possible role in parturition.

| Tissue source | miRNAs | Trend with gestational age | Principal findings/roles in parturition | Ref. | Reported in MSCs [Ref.]
|---------------|--------|---------------------------|----------------------------------------|-----|-------------------------|
| Placenta      | let-7 family | Upregulated | Involved in | [125] | [126] |
|               | let-7 family |             | • Regulation of innate/adaptive immune responses |     |             |
|               | let-7 family |             | • Induction of cell differentiation |     |             |
|               | miR-29a    | Upregulated | • Function as tumor suppressors |     |             |
|               | miR-195    | Downregulated | May contribute to inflammation and senescence aspects of parturition | [127] |             |
|               | miR-181c   | Downregulated | PL2G4B in decidual cells. PL2G4B plays important role in PG biosynthesis at parturition | [128] | [129] |
| Chorio-amniotic | miR-338    | Downregulated | Increases gene and protein expression of PLA2G4B in decidual cells. PLA2G4B plays important role in PG biosynthesis at parturition | [130] |             |
|               | Dicer¹     |             | • Key miRNA-processing enzyme, may contribute to changes in miRNAs processing during labor at term |     |             |
| Reflected amnion² | miR-143    | Downregulated | Higher expression in amnion mesenchymal cells than amnion epithelial cells | [131] | [132] |
| Myometrium    | miR-199a-3p | Downregulated | Increases expression of PTGS2, key enzyme in PG synthesis | [133] | miR199a [135] |
|               | miR-214    | Downregulated | Activated by progesterone, and inhibited by estrogen, mediating opposite effects of these hormones during labor |     |             |
|               | miR-146b-3p| Upregulated | Upregulated both in spontaneous and oxytocin-induced labor | [134] | miR-146b-5p [133] |
|               | miR-200 family | Upregulated | Potentially gene target in myometrium: IL8, NFκB, TLR2, TLR4, BCL2A1, regulating the inflammatory process of labor | [136] | miR200b [135] |
|               | miR-223    | Downregulated | Reduces expression of the transcription factors zinc finger E-box binding homeobox proteins ZEB1 and ZEB2 | [137] |             |
|               | miR-34b    | Downregulated | • ZEB1 and ZEB2 reduce expression of contraction associated genes, oxytocin receptor and gap junction protein alpha 1, and inhibit oxytocin-induced contractility in human myometrial cells |     |             |
|               | miR-34c    | Downregulated | Modulating the uterine quiescence and contractility during labor | [138] | [139] |
| Cervix        | miR-223    | Upregulated | • Regulates genes involved in cervical remodeling during labor, e.g., TLR3, CLDN8, and CALML3 (downregulated after labor) | [138] | [139] |
|               | miR-34b    | Downregulated | TLR is involved in inflammatory signaling of labor |     |             |
|               | miR-34c    | Downregulated | • CLDN8 is the key component of tight junction in cervix epithelium |     |             |
|               |           |             | • Calmodulin suppresses synthesis of matrix metalloproteinases and collagenases |     |             |

¹Amnion that encloses the fetus but is not attached to the placental disk and umbilical cord.
²Amnion that encloses the fetus but is not attached to the placental disk and umbilical cord.
³Has not been reported.

Animal-based studies also have fewer ethical constraints (e.g., where tissue biopsy of the decidua throughout different gestational age can be performed), which allows regular, tight control and monitoring, and precise time-point experimental procedures with the least possible medical intervention and sample variation. Nevertheless, human parturition is a complex and unique process, and thus, most animals are limited in their ability to precisely model human parturition. The findings in animals cannot be readily extrapolated to humans because of the many environmental and functional differences between humans and animal models, in terms of parturition and ageing [119, 120]. For example, human decidualization occurs in response to the hormonal changes released by the corpus luteum at the luteal phase, with or without pregnancy. In contrast, mice do not have a luteal phase in their estrous cycle, and decidualization can only occur after mating [118]. Since the effect of those differences on the outcomes of the studies is unknown, animal studies, e.g., ageing–parturition studies of the murine decidua [3], still require confirmation in human-derived tissues [121].

The human placenta is ideally suited to study ageing-associated parturition features as it contains both of the maternal (decidual) and fetal (chorionic villi) components of the gestational tissues at parturition [122]. There are many advantages in using the human placenta to study ageing-associated parturition features in the decidua. Firstly, it allows studies directly on human decidual tissue that is attached to the maternal side of the placenta. Therefore, changes or specific
functions can be directly measured in the tissue, making it more reflective of the in vivo condition. Human placenta are abundantly available, and their collection does not require invasive procedures or raise any significant ethical constraints (compared with tissue biopsy of human decidua) as it is naturally expelled at the end of pregnancy [123]. Moreover, human placenta also serve as an abundant source of DMSCs [98, 124], which as explained above, may play significant roles in initiating parturition.

However, the use of human placenta in ageing–parturition studies has some limitations. The use of human placenta only allows for a narrow range of time-point observation as it is impractical and unethical to obtain the samples early in uncomplicated pregnancies. The placenta from spontaneous preterm delivery can be used for this purpose, but their potential pathological properties should be taken into consideration as possible confounding factors in assessing spontaneous labor mechanisms. Moreover, patient-to-patient variation, as well as the numerous medical interventions performed to ensure the safety of the mother and neonate during parturition, are inevitable and difficult to control. Nonetheless, ageing–parturition studies on human-derived decidua should be encouraged to validate the findings from animal-based studies.

Conclusion

Ageing propels the gestational clocks to parturition. In the decidua, the ageing process of stromal cells, as well as their corresponding stem cell population (i.e., DMSCs), may contribute to the initiation and/or facilitate various stages of labor. Among many future research questions posed in this review, priority should be given to determining the threshold of ageing features in the decidua, above which are likely to be associated with adverse pregnancy outcome. This information may prove important for developing diagnostic tools and biomarkers. For example, studies could compare the degree of senescence in normal and pathological parturition by measuring the ratio of senescent marker (e.g., p53 MAPK) levels in decidua tissue (or in specific cell type, e.g., DSCs or DMSCs) and in maternal plasma at various gestation ages. Another priority for research is to manipulate the decidual clock using inhibitors of specific molecular pathways of parturition in the decidua (e.g., rapamycin with mTORC1) to produce the optimal pregnancy outcome. Finally, it is essential that the findings of animal models be assessed in human-derived tissue and cell culture studies.

Authors’ roles

JCW wrote the manuscript and prepared the figures, while RK, HMG, and BK critically revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

JCW, HMG, and BK declare that there are no potential conflicts of interest with respect to the authorship, and/or publication of this article. RK was subsequently employed by Exopharm Limited after the preparation of this article.

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