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Current topic

Aging of intrauterine tissues in spontaneous preterm birth and preterm premature rupture of the membranes: A systematic review of the literature

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ABSTRACT

Background: Many adverse pregnancy outcomes (APOs), including spontaneous preterm birth (PTB), are associated with placental dysfunction. Recent clinical and experimental evidences suggest that premature aging of the placenta may be involved in these events. Although placental aging is a well-known concept, the mechanisms of aging during normal pregnancy and premature aging in APOs are still unclear. This review was conducted to assess the knowledge on placental aging related biochemical changes leading to placental dysfunction in PTB and/or preterm premature rupture of membranes (pPROM).
Methods: We performed a systematic review of studies published over the last 50 years in two electronic databases (Pubmed and Embase) on placental aging and PTB or pPROM.
Results: The search yielded 554 citations, 30 relevant studies were selected for full-text review and three were included in the review. Only one study reported oxidative stress-related aging and degenerative changes in human placental membranes and telomere length reduction in fetal cells as part of PTB and/or pPROM mechanisms. Similarly, two animal studies reported findings of decidual senescence and referred to PTB mechanisms.
Conclusion: Placental and fetal membrane oxidative damage and telomere reduction are linked to premature aging in PTB and pPROM but the risk factors and biomolecular pathways causing this phenomenon are not established in the literature. However, no biomarkers or clinical indicators of premature aging as a pathology of PTB and pPROM have been reported. We document major knowledge gaps and propose several areas for future research to improve our understanding of premature aging linked to placental dysfunction.

1. Introduction

The concept of placental aging as pregnancy progresses is not novel and has been reported in animal models and in human placentae since the early 1970s [1–3]. As placental growth continues throughout gestation to accommodate the increasing demands of the growing fetus, rapidly replicating placental cells start to age as pregnancy reaches term. Therefore, placental aging is a physiologic phenomenon and a regular adaptive response [1,4]. From early pregnancy to term, placental cells undergo morphologic changes, such as piknotic and grouped nuclei [3], accumulated fibrinoid [2] and oxidatively modified nucleic acids [1], which are indicative of programmed senescence (aging) of placental tissues at term. Recent findings have also shown that placental syncytiotrophoblast exhibit multiple markers of cellular senescence that might contribute to physiological placental function by maintaining cellular viability during pregnancy [5]. Romero et al. [6] has recently highlighted the importance of maternal decidual cell senescence as a potential mechanistic event in preterm birth.

Aging is an irreversible process, unlike apoptosis (programmed cell death), and can elicit an inflammatory response [7]. In placenta

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or fetal membrane, aging and associated inflammation leads to the production of uterotonins, which, in turn, may trigger labor and subsequent delivery [4,8]. As pregnancy advances, the production of reactive oxygen species (ROS) increases due to the higher metabolic demands of the growing fetus and maximum production occurs prior to term delivery [9–11]. It has been hypothesized that increasing of ROS causes oxidative stress damage that can contribute to placental aging in animals [12] and senescence in human amniotic cells [13]. Premature aging can occur when the intrauterine cavity is exposed to an abnormal environment or to chemical substances that generate oxidative stress thus contributing to placental dysfunction [14,15]. Few studies have investigated the association between adverse pregnancy outcomes (APOs) and placental aging and/or oxidative stress [16–19]. The most studied aging biomarker is the reduction of telomeres, the nucleotide sequences that caps the end of the chromosome and protects it from damage [20]. Shorter telomeres have been reported in trophoblasts from pregnancies with preeclampsia and intrauterine growth restriction, compared to uncomplicated pregnancies [16]. Moreover, oxidative stress and DNA damage to telomeric ends, as well as decreased telomerase activity can lead to premature placental aging and these findings have been implicated in the etiology of intrauterine growth restriction [18,19].

PTB and/or pPROM are likely to be associated with premature placental aging as well as endocrine and immune dysfunctions [10,17,21]. Premature placental aging is also intensified by redox imbalances (balance between pro and antioxidants) reported in these cases [15,22–24] which might lead to oxidative stress damage and placental dysfunction. This systematic review of the literature aimed to identify, critically appraise and synthesize the findings of studies that investigated the association between biological markers of placental aging and PTB and/or pPROM. Mapping the existing knowledge about this question is an essential first step to propose a rational research agenda to fill gaps in this area.

2. Methods

2.1. Types of studies

Studies that investigated the association between biological markers for placental and/or fetal membrane aging and PTB or pPROM were eligible for inclusion in the review. Both *in vivo* and *ex vivo* studies were included. All types of observational study design (cross-sectional, cohort or case-control) were eligible for inclusion.

2.2. Participants

Studies enrolling symptomatic or asymptomatic women of any parity, race, age or socioeconomic background were eligible for inclusion in the review, as long as they provided data on biological biomarkers of placental aging and PTB and/or pPROM. Studies including only multiple pregnancies were excluded.

2.3. Assessment of placental aging

Studies using any method or approach to assess placental aging were eligible, including molecular markers of aging, (e.g. telomere length), cell cycle arrest and cell death biomarkers or histology reports. We excluded genetic studies (genetic syndromes or diseases, polymorphisms) and *in vitro* intrauterine cell culture based studies of aging/cell death/apoptosis related biomarkers not linked to aging or senescence as outcome.

2.4. Outcomes

In order to create a homogeneous group of studies restricted to spontaneous PTB and or pPROM with unknown etiology and to avoid confounding by known risk factors for these outcomes, we excluded studies where 1) PTB or pPROM was associated with other complications of pregnancy (e.g. preeclampsia, intrauterine growth restriction, stillbirth, diabetes or abruptio placenta, among others), 2) Provider initiated preterm births (induced labor or elective preterm cesarean delivery); and 3) studies where PTB was associated with infection or chorioamnionitis.

2.5. Search strategy and study selection

We sought studies published between January 01 1960 and March 31 2014 reporting data on placental and/or fetal membrane aging and PTB and/or pPROM. The following search terms and synonyms were used, adapted to each electronic database: (Aging OR Senescence OR cell aging) AND (Placenta OR fetal membranes OR Extraembryonic Membranes OR placenta diseases OR placental insufficiency OR Decidua OR Trophoblasts OR placentation OR) AND (chorioamnionitis OR Fetal Membranes, Premature Rupture OR Obstetric Labor, Premature OR Premature rupture of membranes OR Amniotic Fluid OR pregnancy complications OR Pregnancy Outcome).

The search was conducted without language restriction in two electronic databases (PUBMED and EMBASE) via OVID. All citations identified were downloaded into electronic reference software (Mendeley, Inc) and duplicates were excluded. The titles and abstract of unique citations were screened and potentially relevant studies were selected for full-text reading; those that fulfilled the selection criteria were included in the review. The search was complemented by screening the reference lists of included studies.

The process of study selection was performed in duplicate by two independent reviewers. Discrepancies were discussed until consensus was reached.

2.6. Data extraction and quality assessment

A specific data extraction form was created to collect the following data from each included study: objectives and design, number and characteristics of participants, outcome phenotype definition, type of biological sample, biological markers used and details of the technique, results (association between marker and PTB or pPROM).

The quality of studies was assessed based on the description of study protocol and molecular and histologic markers and their relevance pertaining to aging. These domains were graded as poor, adequate or good. Data extraction and quality assessment were performed in duplicate by two independent reviewers. Results were compared, discrepancies were discussed until consensus was reached and a single final extraction and quality assessment form was obtained for each study.

3. Results

The initial search identified 554 unduplicated references, 524 of which were excluded at first screening and 30 potentially relevant citations were selected for full-text reading. Three studies fulfilled the selection criteria and were included in the review (Fig. 1).

Table 1 presents the main characteristics of the included studies. Menon et al. [25] collected umbilical blood from 132 infants delivered vaginally or by cesarean from three groups: 35 healthy term controls (mean gestational age 268.1 ± 20.1 days), 69 PTB with intact membranes (mean gestational age 213.9 ± 37.4 days) and 28 pPROM (mean gestational age 210.3 ± 24.2 days). The investigators assessed the lengths of telomere in fetal leukocytes and correlated these with lengths of telomeres in placental membranes (normal term births, n = 08, PTB, n = 05; pPROM, n = 05). The longest telomeres were found in fetal leucocyte in cases of PTB with intact membranes whereas cases at term or with pPROM presented similar results. Telomere lengths in placental membranes showed the same trends in pPROM and PTB as observed in fetal leucocytes: placental membrane telomeres were shorter in pPROM compared to PTB, whereas no differences were seen between pPROM and term birth. Despite the small sample size, there was a strong correlation between placental membrane and fetal DNA telomere lengths (Pearson's test r = 0.77; p, 0.01), suggesting premature aging of fetal cells and tissues in pPROM. Fetal telomere lengths were significantly shorter in pPROM than in PTB of same gestational age, suggesting different pathways underlying the pathophysiologies of pPROM and PTB. This study provided all the details regarding participant characteristics and methodology and was therefore assessed as being of good quality.

The other two included studies are animal model studies. Burnum et al. [26] reported down-regulation of an antioxidant enzyme cluster in decidua from p53-deficient mice ($p53^{d/d}$). These results suggest that $p53^{d/d}$ deciduae with decreased expression of antioxidant enzymes are susceptible to OS, which in turn compromises decidualization and induces premature senescence, ultimately triggering preterm birth in $p53^{d/d}$ decidua. In this study, more than 50% of $p53^{d/d}$ females had preterm birth with neonatal death due to