



Published in final edited form as:

Placenta Reprod Med. 2022 July 6; 1: . doi:10.54844/prm.2022.0104.

Fetal membrane at the feto-maternal interface: An underappreciated and understudied intrauterine tissue

Lauren Richardson,

Ramkumar Menon

Department of Obstetrics & Gynecology, Division of Basic Science and Translational Research, The University of Texas Medical Branch at Galveston, Galveston 77555, TX, USA

INTRODUCTION

While most intrauterine tissues are thoroughly studied for their role in pregnancy maintenance and their contribution to labor initiation, the fetal membranes (*i.e.*, amniochorionic membranes) are primarily overlooked.^[1,2] The fetal membrane lines the intrauterine cavity (Figure 1A) and provides critical mechanical, immune, and endocrine support to protect the fetus during gestation^[1,3–12] and has been shown to provide vital labor initiating signaling at term and preterm.^[2,5,13–20] The function of the fetal membrane is derived from its unique makeup of multiple collagen layers,^[21–23] along with fetal-derived cells that line with maternal decidua, forming the feto-maternal interface. A summary of the structure and function of the fetal membranes and the challenges researchers face studying this tissue are described below.

FETAL MEMBRANE ANATOMY

The fetal membrane and the maternal decidua form one of the feto-maternal interfaces during gestation (Figure 1B). The fetal membrane comprises two epithelial membranes, the amnion, and chorion, that are connected by collagen-rich multiple layers of extracellular matrix.^[2,24] The amnion membrane, which maintains most of the fetal membranes' tensile strength,^[10,11,25–29] consists of an amnion epithelial layer connected to the fibrous-spongy layer of the extracellular matrix via a Type IV collagen-rich basement membrane.^[22,23] These collagen layers contain various stromal cell types, including amnion mesenchymal cells, fibroblasts, immune cells, and chorion mesenchymal cells.^[30–34] Stromal cells within the fetal membrane secrete Type I and III collagens to create a variety of extracellular matrix layers, forming a fibrous skeleton responsible for maintaining membrane integrity.^[22,35] The chorion membrane plays a crucial role in immune tolerance.^[36–38] It contains the reticular layer and connects to the chorion trophoblast cells through another Type IV

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 Unported License, which allows others to copy and redistribute the material in any medium or format non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Corresponding Author: Prof. Ramkumar Menon, ra2menon@utmb.edu.

Conflict of Interest

Ramkumar Menon is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member and her research group.

collagen-rich basement membrane.^[39,40] These fetal membrane layers are fused with the maternal decidua parietalis containing leukocytes to form the feto-maternal interface during pregnancy.^[24,41–43]

REGIONS OF THE FETAL MEMBRANE

The fetal membranes are divided into different regions based on their proximity to maternal or fetal organs. They are generally divided into a region lining the placental bed (*i.e.*, the region lining the apical side of the placenta), or reflective membranes that line the intrauterine cavity.^[44,45] Though they have similar architecture, the membrane lining of the placental bed contains a condensed extracellular matrix and chorion layer. It only includes a small portion of the overall surface area of the fetal membrane.^[46] Furthermore, the reflective membranes can be classified as the peri-placental zone (*i.e.*, two–three inches from the placenta), mid-zone (*i.e.*, middle and largest region), and cervical zone (*i.e.*, overlaying the cervix) depending on their proximity to the placenta or the cervix.^[44,45] Within the cervical zone is a region of the fetal membrane termed the zone of altered morphology (ZAM) which contains loose collagen structures that may contribute to the rupture of the membranes at term.^[21,47,48] A better understanding of the region from which membranes are sampled and its histology is essential when studying fetal membrane structure and its cellularity and function.

FETAL MEMBRANE FUNCTION DURING GESTATION AND PARTURITION

The fetal membrane is not an inert tissue that lines the maternal decidua or the inner uterine cavity, instead, it is a complex multicellular organ that plays a distinct and vital role in maintaining pregnancy and the onset of labor signaling.^[49] Throughout gestation, the amnion component of the fetal membrane plays a critical role in sustaining membrane integrity by undergoing cellular remodeling.^[4,50–53] This process upholds the amnion tensile strength providing a watertight barrier and structure to the intrauterine cavity. The chorion component of the fetal membrane plays a distinct role from the amnion, as it is responsible for creating immune homeostasis in various ways. Chorion trophoblast cells modulate the immune environment by producing anti-inflammatory hormones^[9,36,54,55] and cytokines,^[12] and by buffering maternal (decidual) immune cell invasion^[47,56] and immune intolerance by abundant expression of human leukocyte antigen G (HLA-G).^[3] These endocrine and paracrine signalers help to maintain immune cell homeostasis at the choriodecidual interface.^[12,57]

At term, close to 40 weeks gestation, both fetal and maternal tissue contribute to an increased inflammatory load and immune cell activation that promotes myometrial contractions and cervical ripening leading to delivery of the baby.^[1,2,20,58] The fetal membrane has been recently shown to play a substantial role in initiating this labor cascade.^[2,17,20] Traditionally, it is known that fetal membranes produce cyclooxygenase-2 and prostaglandins that contribute to membrane weakening and rupture at term.^[59–64] Recent studies suggest that fetal membranes from both humans and mice undergo a reactive oxygen species induced (due to intrauterine oxidative stress at term), telomere-dependent, activation of p38 mitogen-activated protein kinase (p38MAPK).^[24,31,65–68] p38MAPK is a stress

signaler that can contribute to various cell fates.^[66,69,70] Increased p38MAPK activation at term causes fetal membrane senescence, or a mechanism of tissue aging, and secretion of senescence-associated secretory phenotypes (SASP) comprised of pro-inflammatory cytokines, chemokines, growth factors, cell-free fetal DNA, and matrix metalloproteinases.^[24,29,34,54,71,72] SASP represents sterile inflammation in fetal tissues that propagates to the maternal side and transitions the quiescent myometrium and cervix into a contractile (active/labor) phenotype. This induction of stress-activated p38MAPK also causes fetal membrane epithelial cells (*i.e.*, amnion and chorion) to undergo cellular transitions (*i.e.*, epithelial-to-mesenchymal transition or EMT).^[5,50,52,53,73] EMT increases the number of mesenchymal cells, promotes collagen degradation, and changes the inflammatory status at the feto-maternal interface.^[50,73] These mesenchymal cells promote collagen degradation by increasing matrix metalloproteinases nine that can contribute to the development of microfractures (*i.e.*, biologic fissures) within the extracellular matrix of the membranes.^[17,40,53] It is postulated that these pro-labor inflammatory signals described above could propagate in two different ways: diffusion through microfractures or exosomes (30–160 nm size extracellular vesicles) released from fetal membrane cells. Microfractures are higher in number and morphometrically (width and length) at term.^[17,40,53] Experimentally, we have recapitulated that *in vitro* conditions mimicking labor also increases appearance of microfractures with larger and deeper features.^[17,40,53] This suggests their relevance in the propagation of parturition signals. Exosomes are capable of carrying contents from the cell of their origin. It is reported that exosome cargo from oxidatively stressed fetal membrane cells contains active forms of p38MAPK and SASPs capable of promoting labor signaling.^[14,16,74–76]

CHALLENGES STUDYING FETAL MEMBRANES

Researchers studying fetal membranes must overcome many obstacles to rationalize the importance of studying their tissue of interest to journal editors and funding agencies. The first hurdle they must overcome is the definition of the fetal membrane and the second is to convince reviewers that the fetal membranes are separate from the placenta. Heterogeneity in the nomenclature of the membranes (*i.e.*, amniotic sac, amniochorionic membrane, fetal membrane, placental membrane, feto-maternal interface) and which cell layers should be included in this terminology creates ambiguity.

The Fetal Membrane Society (FMS) is formed to educate reproductive biologists and perinatal biologists and scientists on the relevance and significance of the membranes. FMS is also involved in creating awareness of the importance of fetal membrane research among the public. As a major contributor to pregnancy maintenance and a determining factor in the timing of birth at term and preterm. As a contributor to fetal signals of parturition, regulating its pathological functions is critical to reducing the incidences of preterm birth. This topic was one of great interest at this year's FMS meeting held during the 2022 Society of Reproductive Investigation International meeting. The FMS concluded that a white paper should be published to define "fetal membranes" and standardize the nomenclature in the literature. The hope is that a set nomenclature will improve reproducibility and provide clarity when documenting the important role, the fetal membranes play during gestation and parturition. Additionally, the fetal membranes are classically misidentified as an extension of

the placenta. As it is well known now, the fetal membranes are not a mere extension of the placenta but play very important mechanical, immune, endocrine, and communication roles between the mother and fetus.^[1] These functions regulate membrane growth and maturation which contributes to pregnancy homeostasis. Misclassification of the membranes and not identifying them as a distinct tissue from the placenta has slowed fetal membrane-specific research and funding. This and the lack of an advocacy group or international organization that focuses on this topic have restricted scientific awareness of this fascinating tissue. The FMS has been trying to address some of these issues and developing strategies to generate awareness and fill knowledge gaps in fetal membrane biology and function.

Unlike other intrauterine tissues such as the myometrium or placenta, that have established *in vitro* methodology such as commercially available cell lines, *ex vivo* systems (*i.e.*, myograph and placenta perfusion),^[77–80] organoids,^[81,82] organ-on-chip devices,^[83–88] and validated animal models, the fetal membranes lack a majority of these resources. Currently, there are no commercially available and validated iPS or cell lines for the amnion, chorion, or the decidua of the fetal membrane feto-maternal interface. Due to this, researchers are forced to use either contaminated (*i.e.*, amnion wish cells – HeLa) or improper cell types (*i.e.*, placenta choriocarcinoma – BeWo to mimic the chorion trophoblasts; decidualized endometrium to mimic the decidua parietalis) to conduct cellular studies. This limits research undertaken in the field and reduces new discoveries. Furthermore, unlike the other organs described above, very few organ-on-chip models of the fetal membranes exist,^[46,52,89–91] and fetal membrane organoids are yet to be developed. These are both critical platforms needed in this field to truly understand cell-cell cell-collagen interactions responsible for pregnancy maintenance and pathology onset.

SUMMARY

The fetal membranes form a unique barrier that surrounds the neonate and promotes its survival during gestation. This membrane is comprised of two components, the amnion and chorion layers, that function as distinctly unique epithelial compartments promoting homeostasis during development. At term initiated by physiological signals, or preterm induced by pathology, these layers promote signaling cascades that contribute to labor onset. Advanced *in vivo* and *in vitro* methodology to study the fetal membrane, along with the formation of advocacy groups, are needed to truly understand and promote this unique tissue.

CONCLUSIONS

If studied adequately, the fetal membranes, as one of the feto-maternal interfaces, could answer many questions regarding labor induction, inflammation, infection, and pathologies that lead to preterm birth. A better understanding of all aspects of fetal membrane origin, as well as cellular characteristics, needs to be taken into account to tease out the mechanism behind the labor cascade and how to target said pathways therapeutically. A global understanding of the role of fetal membranes in parturition highlights the critical function of the membranes during pregnancy and in the prevention of adverse pregnancy outcomes.

Source of Funding

This study was supported by R01HD100729-01S1 (NIH/NICHD) and UG3TR003283 (NCATS/NICHD) to Dr. Ramkumar Menon and Dr. Arum Han. Dr. Richardson is supported by a research career development award (K12HD052023: Building Interdisciplinary Research Careers in Women's Health Program-BIRCWH; Berenson, PI) from the National Institutes of Health/Office of the Director (OD)/National Institute of Allergy and Infectious Diseases (NIAID), and Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

1. Menon R, Moore JJ. Fetal membranes, not a mere appendage of the placenta, but a critical part of the fetal-maternal interface controlling parturition. *Obstet Gynecol Clin North Am* 2020;47:147–162. [PubMed: 32008665]
2. Menon R, Richardson LS, Lappas M. Fetal membrane architecture, aging and inflammation in pregnancy and parturition. *Placenta* 2019;79:40–45. [PubMed: 30454905]
3. Tantengco OAG, Richardson L, Lee A, Kammala A, Silva MC, Shahin H, et al. Histocompatibility antigen, class I, G (HLA-G)'s role during pregnancy and parturition: A systematic review of the literature. *Life (Basel)* 2021;11:1061. [PubMed: 34685432]
4. Richardson LS, Menon PR, Menon R. The effects of extracellular matrix rigidity on 3-dimensional cultures of amnion membrane cells. *Placenta* 2020;90:82–89. [PubMed: 32056556]
5. Richardson LS, Radnaa E, Urrabaz-Garza R, Lavu N, Menon R. Stretch, scratch, and stress: Suppressors and supporters of senescence in human fetal membranes. *Placenta* 2020;99:27–34. [PubMed: 32750642]
6. Marques CF, Diogo GS, Pina S, Oliveira JM, Silva TH, Reis RL. Collagen-based bioinks for hard tissue engineering applications: a comprehensive review. *J Mater Sci Mater Med* 2019;30:32. [PubMed: 30840132]
7. Joyce EM, Diaz P, Tamarkin S, Moore R, Strohl A, Stetzer B, et al. In vivo stretch of term human fetal membranes. *Placenta* 2016;38:57–66. [PubMed: 26907383]
8. Kumar D, Moore RM, Mercer BM, Mansour JM, Redline RW, Moore JJ. The physiology of fetal membrane weakening and rupture: Insights gained from the determination of physical properties revisited. *Placenta* 2016;42:59–73. [PubMed: 27238715]
9. Kumar D, Springel E, Moore RM, Mercer BM, Philipson E, Mansour JM, et al. Progesterone inhibits in vitro fetal membrane weakening. *Am J Obstet Gynecol* 2015;213:520.e1–9.
10. Mauri A, Perrini M, Ehret AE, De Focatiis DSA, Mazza E. Timedependent mechanical behavior of human amnion: macroscopic and microscopic characterization. *Acta Biomater* 2015;11:314–323. [PubMed: 25240983]
11. Perrini M, Mauri A, Ehret AE, Ochsenbein-Kölbl N, Zimmermann R, Ehrbar M, et al. Mechanical and microstructural investigation of the cyclic behavior of human amnion. *J Biomech Eng* 2015;137:061010. [PubMed: 25780908]
12. Hadley EE, Richardson LS, Torloni MR, Menon R. Gestational tissue inflammatory biomarkers at term labor: A systematic review of literature. *Am J Reprod Immunol* 2018;79:10.1111/aji.12776.
13. Radnaa E, Richardson LS, Sheller-Miller S, Baljinnyam T, de Castro Silva M, Kumar Kammala A, et al. Extracellular vesicle mediated fetomaternal HMGB1 signaling induces preterm birth. *Lab Chip* 2021;21:1956–1973. [PubMed: 34008619]
14. Sheller-Miller S, Trivedi J, Yellon SM, Menon R. Exosomes cause preterm birth in mice: Evidence for paracrine signaling in pregnancy. *Sci Rep* 2019;9:608. [PubMed: 30679631]
15. Menon R. Initiation of human parturition: signaling from senescent fetal tissues via extracellular vesicle mediated paracrine mechanism. *Obstet Gynecol Sci* 2019;62:199–211. [PubMed: 31338337]
16. Hadley EE, Sheller-Miller S, Saade G, Salomon C, Mesiano S, Taylor RN, et al. Amnion epithelial cell-derived exosomes induce inflammatory changes in uterine cells. *Am J Obstet Gynecol* 2018;219:478.e1–478.e21.

17. Menon R, Richardson LS. Preterm prelabor rupture of the membranes: A disease of the fetal membranes. *Semin Perinatol* 2017;41:409–419. [PubMed: 28807394]
18. Menon R, Behnia F, Poletini J, Saade GR, Campisi J, Velarde M. Placental membrane aging and HMGB1 signaling associated with human parturition. *Aging* 2016;8:216–230. [PubMed: 26851389]
19. Dutta EH, Behnia F, Boldogh I, Saade GR, Taylor BD, Kacerovský M, et al. Oxidative stress damage-associated molecular signaling pathways differentiate spontaneous preterm birth and preterm premature rupture of the membranes. *Mol Hum Reprod* 2016;22:143–157. [PubMed: 26690900]
20. Menon R, Bonney EA, Condon J, Mesiano S, Taylor RN. Novel concepts on pregnancy clocks and alarms: redundancy and synergy in human parturition. *Hum Reprod Update* 2016;22:535–560. [PubMed: 27363410]
21. Mauri A, Perrini M, Mateos JM, Maake C, Ochsenbein-Koelble N, Zimmermann R, et al. Second harmonic generation microscopy of fetal membranes under deformation: normal and altered morphology. *Placenta* 2013;34:1020–1026. [PubMed: 24070621]
22. Strauss JF 3rd. Extracellular matrix dynamics and fetal membrane rupture. *Reprod Sci* 2013;20:140–153. [PubMed: 22267536]
23. Malak TM, Ockleford CD, Bell SC, Dalgleish R, Bright N, Macvicar J. Confocal immunofluorescence localization of collagen types I, III, IV, V and VI and their ultrastructural organization in term human fetal membranes. *Placenta* 1993;14:385–406. [PubMed: 8248033]
24. Menon R. Human fetal membranes at term: Dead tissue or signalers of parturition? *Placenta* 2016;44:1–5. [PubMed: 27452431]
25. Chowdhury B, David AL, Thrasivoulou C, Becker DL, Bader DL, Chowdhury TT. Tensile strain increased COX-2 expression and PGE2 release leading to weakening of the human amniotic membrane. *Placenta* 2014;35:1057–1064. [PubMed: 25280972]
26. Jabareen M, Mallik AS, Bilic G, Zisch AH, Mazza E. Relation between mechanical properties and microstructure of human fetal membranes: an attempt towards a quantitative analysis. *Eur J Obstet Gynecol Reprod Biol* 2009;144:S134–S141. [PubMed: 19282091]
27. Joyce EM, Moore JJ, Sacks MS. Biomechanics of the fetal membrane prior to mechanical failure: review and implications. *Eur J Obstet Gynecol Reprod Biol* 2009;144:S121–S127. [PubMed: 19303191]
28. Kendal-Wright CE, Hubbard D, Bryant-Greenwood GD. Chronic stretching of amniotic epithelial cells increases pre-B cell colony-enhancing factor (PBEF/visfatin) expression and protects them from apoptosis. *Placenta* 2008;29:255–265. [PubMed: 18272217]
29. Kendal-Wright CE. Stretching, mechanotransduction, and proinflammatory cytokines in the fetal membranes. *Reprod Sci* 2007;14:35–41. [PubMed: 18089608]
30. Uchide N, Ohyama K, Bessho T, Takeichi M, Toyoda H. Possible roles of proinflammatory and chemoattractive cytokines produced by human fetal membrane cells in the pathology of adverse pregnancy outcomes associated with influenza virus infection. *Mediators Inflamm* 2012;2012:270670. [PubMed: 22899878]
31. Jin J, Richardson L, Sheller-Miller S, Zhong N, Menon R. Oxidative stress induces p38MAPK-dependent senescence in the feto-maternal interface cells. *Placenta* 2018;67:15–23. [PubMed: 29941169]
32. Rogers LM, Anders AP, Doster RS, Gill EA, Gnecco JS, Holley JM, et al. Decidual stromal cell-derived PGE2 regulates macrophage responses to microbial threat. *Am J Reprod Immunol* 2018;80:e13032. [PubMed: 30084522]
33. Boldenow E, Jones S, Lieberman RW, Chames MC, Aronoff DM, Xi C, et al. Antimicrobial peptide response to group B Streptococcus in human extraplacental membranes in culture. *Placenta* 2013;34:480–485. [PubMed: 23562109]
34. Sato BL, Collier ES, Vermudez SA, Junker AD, Kendal-Wright CE. Human amnion mesenchymal cells are pro-inflammatory when activated by the Toll-like receptor 2/6 ligand, macrophage-activating lipoprotein-2. *Placenta* 2016;44:69–79. [PubMed: 27452440]
35. Parry S, Strauss JF 3rd. Premature rupture of the fetal membranes. *N Engl J Med* 1998;338:663–670. [PubMed: 9486996]

36. Feng L, Allen TK, Marinello WP, Murtha AP. Roles of progesterone receptor membrane component 1 in oxidative stress—induced aging in chorion cells. *Reprod Sci* 2019;26:394–403. [PubMed: 29783884]
37. McQuilling JP, Vines JB, Kimmerling KA, Mowry KC. Proteomic comparison of amnion and chorion and evaluation of the effects of processing on placental membranes. *Wounds* 2017;29:E36–E40.
38. PrabhuDas M, Bonney E, Caron K, Dey S, Erlebacher A, Fazleabas A, et al. Immune mechanisms at the maternal-fetal interface: perspectives and challenges. *Nat Immunol* 2015;16:328–334. [PubMed: 25789673]
39. Verbruggen SW, Oyen ML, Phillips ATM, Nowlan NC. Function and failure of the fetal membrane: Modelling the mechanics of the chorion and amnion. *PLoS One* 2017;12:e0171588. [PubMed: 28350838]
40. Richardson L, Vargas G, Brown T, Ochoa L, Trivedi J, Kacerovský M, et al. Redefining 3Dimensional placental membrane microarchitecture using multiphoton microscopy and optical clearing. *Placenta* 2017;53:66–75. [PubMed: 28487023]
41. Aronoff DM. Deconstructing extraplacental membranes to understand bacterial chorioamnionitis. *Trans Am Clin Climatol Assoc* 2020;131:72–79. [PubMed: 32675845]
42. Anders AP, Gaddy JA, Doster RS, Aronoff DM. Current concepts in maternal-fetal immunology: Recognition and response to microbial pathogens by decidual stromal cells. *Am J Reprod Immunol* 2017;77:10.1111/aji.12623.
43. Radnaa E, Urrabaz-Garza R, Elrod ND, de Castro Silva M, Pyles R, Han A, et al. Generation and characterization of human Fetal membrane and Decidual cell lines for reproductive biology experiments. *Biol Reprod* 2022;106:568–582. [PubMed: 34935931]
44. Weidinger A, Požnel L, Wolbank S, Banerjee A. Sub-regional differences of the human amniotic membrane and their potential impact on tissue regeneration application. *Front Bioeng Biotechnol* 2021;8:613804. [PubMed: 33520964]
45. Lemke A, Castillo-Sánchez JC, Proding F, Ceranic A, HennerbichlerLugscheider S, Pérez-Gil J, et al. Human amniotic membrane as newly identified source of amniotic fluid pulmonary surfactant. *Sci Rep* 2017;7:6406. [PubMed: 28743969]
46. Richardson L, Kim S, Menon R, Han A. Organ-on-chip technology: The future of feto-maternal interface research? *Front Physiol* 2020;11:715. [PubMed: 32695021]
47. Marcellin L, Schmitz T, Messaoudene M, Chader D, Parizot C, Jacques S, et al. Immune modifications in fetal membranes overlying the cervix precede parturition in humans. *J Immunol* 2017;198:1345–1356. [PubMed: 28031337]
48. Malak TM, Bell SC. Structural characteristics of term human fetal membranes: a novel zone of extreme morphological alteration within the rupture site. *Br J Obstet Gynaecol* 1994;101:375–386. [PubMed: 8018607]
49. Megli CJ, Coyne CB. Infections at the maternal-fetal interface: an overview of pathogenesis and defence. *Nat Rev Microbiol* 2022;20:67–82. [PubMed: 34433930]
50. Richardson LS, Taylor RN, Menon R. Reversible EMT and MET mediate amnion remodeling during pregnancy and labor. *Sci Signal* 2020;13:eaay1486. [PubMed: 32047115]
51. Canciello A, Russo V, Berardinelli P, Bernabò N, Muttini A, Mattioli M, et al. Progesterone prevents epithelial-mesenchymal transition of ovine amniotic epithelial cells and enhances their immunomodulatory properties. *Sci Rep* 2017;7:3761. [PubMed: 28630448]
52. Richardson L, Jeong S, Kim S, Han A, Menon R. Amnion membrane organ-on-chip: an innovative approach to study cellular interactions. *FASEB J* 2019;33:8945–8960. [PubMed: 31039044]
53. Richardson LS, Vargas G, Brown T, Ochoa L, Sheller-Miller S, Saade GR, et al. Discovery and characterization of human amniochorionic membrane microfractures. *Am J Pathol* 2017;187:2821–2830. [PubMed: 28939208]
54. Meng Y, Murtha AP, Feng L. Progesterone, inflammatory cytokine (TNF- α), and oxidative stress (H₂O₂) regulate progesterone receptor membrane component 1 expression in fetal membrane cells. *Reprod Sci* 2016;23:1168–1178. [PubMed: 26919974]
55. Murtha AP, Feng L, Yonish B, Leppert PC, Schomberg DW. Progesterone protects fetal chorion and maternal decidua cells from calcium-induced death. *Am J Obstet Gynecol* 2007;196:257.e1–5.

56. Yang F, Zheng Q, Jin L. Dynamic function and composition changes of immune cells during normal and pathological pregnancy at the maternal-fetal interface. *Front Immunol* 2019;10:2317. [PubMed: 31681264]
57. Kota SK, Gayatri K, Jammula S, Kota SK, Krishna SV, Meher LK, et al. Endocrinology of parturition. *Indian J Endocrinol Metab* 2013;17:50. [PubMed: 23776853]
58. Kim S, Richardson L, Radnaa E, Chen Z, Rusyn I, Menon R, et al. Molecular mechanisms of environmental toxin cadmium at the feto-maternal interface investigated using an organ-on-chip (FMi-OOC) model. *J Hazard Mater* 2022;422:126759. [PubMed: 34391970]
59. Myatt L, Sun K. Role of fetal membranes in signaling of fetal maturation and parturition. *Int J Dev Biol* 2010;54:545–553. [PubMed: 19924634]
60. Zhu XO, Yang Z, Guo CM, Ni XT, Li JN, Ge YC, et al. Paradoxical stimulation of cyclooxygenase-2 expression by glucocorticoids via a cyclic AMP response element in human amnion fibroblasts. *Mol Endocrinol* 2009;23:1839–1849. [PubMed: 19797430]
61. Casciani V, Marinoni E, Bocking AD, Moscarini M, Di Iorio R, Challis JR. Opposite effect of phorbol ester PMA on PTGS2 and PGDH mRNA expression in human chorion trophoblast cells. *Reprod Sci* 2008;15:40–50. [PubMed: 18212353]
62. Lappas M, Permezel M, Rice GE. Mitogen-activated protein kinase proteins regulate LPS-stimulated release of pro-inflammatory cytokines and prostaglandins from human gestational tissues. *Placenta* 2007;28:936–945. [PubMed: 17433832]
63. Park DW, Bae YS, Nam JO, Kim JH, Lee YG, Park YK, et al. Regulation of cyclooxygenase-2 expression by phospholipase D in human amnion-derived WISH cells. *Mol Pharmacol* 2002;61:614–619. [PubMed: 11854442]
64. Duchesne MJ, Thaler-Dao H, de Paulet AC. Prostaglandin synthesis in human placenta and fetal membranes. *Prostaglandins* 1978;15:19–42. [PubMed: 24235]
65. Richardson L, Dixon CL, Aguilera-Aguirre L, Menon R. Oxidative stress-induced TGF- β /TAB1-mediated p38MAPK activation in human amnion epithelial cells. *Biol Reprod* 2018;99:1100–1112. [PubMed: 29893818]
66. Bonney EA. Mapping out p38MAPK. *Am J Reprod Immunol* 2017;77:10.1111/aji.12652.
67. Polettini J, Behnia F, Taylor BD, Saade GR, Taylor RN, Menon R. Telomere fragment induced amnion cell senescence: A contributor to parturition? *PLoS One* 2015;10:e0137188. [PubMed: 26397719]
68. Menon R, Boldogh I, Urrabaz-Garza R, Polettini J, Syed TA, Saade GR, et al. Senescence of primary amniotic cells via oxidative DNA damage. *PLoS One* 2013;8:e83416. [PubMed: 24386195]
69. Menon R, Papaconstantinou J. p38 Mitogen activated protein kinase (MAPK): a new therapeutic target for reducing the risk of adverse pregnancy outcomes. *Expert Opin Ther Targets* 2016;20:1397–1412. [PubMed: 27459026]
70. Gupta J, Nebreda AR. Roles of p38 α mitogen-activated protein kinase in mouse models of inflammatory diseases and cancer. *FEBS J* 2015;282:1841–1857. [PubMed: 25728574]
71. Padron JG, Saito Reis CA, Kendal-Wright CE. The role of danger associated molecular patterns in human fetal membrane weakening. *Front Physiol* 2020;11:602. [PubMed: 32625109]
72. Allen TK, Feng L, Nazzari M, Grotte CA, Buhimschi IA, Murtha AP. The effect of progestins on tumor necrosis factor α -induced matrix metalloproteinase-9 activity and gene expression in human primary amnion and chorion cells in vitro. *Anesth Analg* 2015;120:1085–1094. [PubMed: 25806402]
73. Richardson L, Menon R. Proliferative, migratory, and transition properties reveal metastate of human amnion cells. *Am J Pathol* 2018;188:2004–2015. [PubMed: 29981743]
74. Radnaa E, Richardson LS, Sheller-Miller S, Baljinnayam T, de Castro Silva M, Kumar Kammala A, et al. Extracellular vesicle mediated feto-maternal HMGB1 signaling induces preterm birth. *Lab Chip* 2021;21:1956–1973. [PubMed: 34008619]
75. Sheller-Miller S, Urrabaz-Garza R, Saade G, Menon R. Damage Associated molecular pattern markers HMGB1 and cell-free fetal telomere fragments in oxidative-stressed amnion epithelial cell-derived exosomes. *J Reprod Immunol* 2017;123:3–11. [PubMed: 28858636]

76. Sheller-Miller S, Lei J, Saade G, Salomon C, Burd I, Menon R. Feto-maternal trafficking of exosomes in murine pregnancy models. *Front Pharmacol* 2016;7:432. [PubMed: 27895585]
77. Warth B, Preindl K, Manser P, Wick P, Marko D, Buerki-Thurnherr T. Transfer and metabolism of the xenoestrogen Zearalenone in human perfused placenta. *Environ Health Perspect* 2019;127:107004. [PubMed: 31596610]
78. Gruber MM, Hirschmugl B, Berger N, Holter M, Radulovi S, Leitinger G, et al. Plasma proteins facilitates placental transfer of polystyrene particles. *J Nanobiotechnology* 2020;18:128. [PubMed: 32907583]
79. Roy S, Nanovskaya T, Patrikeeva S, Cochran E, Parge V, Guess J, et al. M281, an anti-FcRn antibody, inhibits IgG transfer in a human ex vivo placental perfusion model. *Am J Obstet Gynecol* 2019;220:498.e1–498.e9.
80. Ong SS, Baker PN, Mayhew TM, Dunn WR. Remodeling of myometrial radial arteries in preeclampsia. *Am J Obstet Gynecol* 2005;192:572–579. [PubMed: 15696005]
81. Horii M, Touma O, Bui T, Parast MM. Modeling human trophoblast, the placental epithelium at the maternal fetal interface. *Reproduction* 2020;160:R1–R11. [PubMed: 32485667]
82. Turco MY, Gardner L, Kay RG, Hamilton RS, Prater M, Hollinshead MS, et al. Trophoblast organoids as a model for maternal-fetal interactions during human placentation. *Nature* 2018;564:263–267. [PubMed: 30487605]
83. Pemathilaka RL, Caplin JD, Aykar SS, Montazami R, Hashemi NN. Placenta-on-a-chip: In vitro study of caffeine transport across placental barrier using liquid chromatography mass spectrometry. *Glob Chall* 2019;3:1800112. [PubMed: 31565368]
84. Pemathilaka RL, Reynolds DE, Hashemi NN. Drug transport across the human placenta: review of placenta-on-a-chip and previous approaches. *Interface Focus* 2019;9:20190031. [PubMed: 31485316]
85. Yin F, Zhu Y, Zhang M, Yu H, Chen W, Qin J. A 3D human placenta-on-a-chip model to probe nanoparticle exposure at the placental barrier. *Toxicol In Vitro* 2019;54:105–113. [PubMed: 30248392]
86. Blundell C, Yi YS, Ma L, Tess ER, Farrell MJ, Georgescu A, et al. Placental drug transport-on-a-chip: A microengineered in vitro model of transporter-mediated drug efflux in the human placental barrier. *Adv Healthc Mater* 2018;7:10.1002/adhm.201700786.
87. Blundell C, Tess ER, Schanzer ASR, Coutifaris C, Su EJ, Parry S, et al. A microphysiological model of the human placental barrier. *Lab Chip* 2016;16:3065–3073. [PubMed: 27229450]
88. Lee JS, Romero R, Han YM, Kim HC, Kim CJ, Hong JS, et al. Placenta-on-a-chip: a novel platform to study the biology of the human placenta. *J Matern Fetal Neonatal Med* 2016;29:1046–1054. [PubMed: 26075842]
89. Richardson LS, Kim S, Han A, Menon R. Modeling ascending infection with a feto-maternal interface organ-on-chip. *Lab Chip* 2020;20:4486–4501. [PubMed: 33112317]
90. Richardson L, Gnecco J, Ding T, Osteen K, Rogers LM, Aronoff DM, et al. Fetal membrane organ-on-chip: An innovative approach to study cellular interactions. *Reprod Sci* 2020;27:1562–1569. [PubMed: 32430706]
91. Gnecco JS, Anders AP, Cliffl D, Pensabene V, Rogers LM, Osteen K, et al. Instrumenting a fetal membrane on a chip as emerging technology for preterm birth research. *Curr Pharm Des* 2017;23:6115–6124. [PubMed: 28847303]

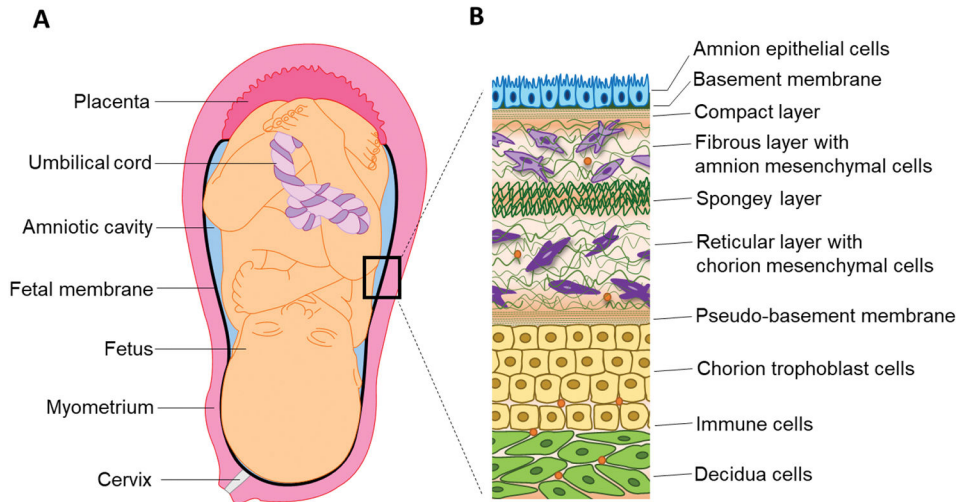


Figure 1.

Intrauterine and fetal membrane anatomy. (A) Within the intrauterine cavity, there are a variety of maternal (*i.e.*, myometrium and cervix) and fetal (*i.e.*, placenta, umbilical cord, and an amniotic cavity containing amniotic fluid, and the fetal membranes) derived organs that surround the fetus and contribute to pregnancy maintenance. The fetal membranes (black) line the cavity and are derived from multiple fetal cellular and collagen layers to form the feto-maternal interface. (B) The amnion epithelial cells (blue) are connected to the basement membrane (dark green) and compact layer (green dashes) of the extracellular matrix (ECM) forming an amniotic fluid-tight barrier. Within the first layer of the ECM (*i.e.*, the fibrous layer), amnion mesenchymal cells (light purple) migrate and interact with the collagen environment. Separating the fibrous and reticular layers of the ECM is the spongy layer that separates the amnion (blue) and chorion (yellow) portions of the fetal membranes. The reticular layer of the ECM contains chorion mesenchymal cells (dark purple) that is connected to the pseudo-basement membrane of the chorion. The multi-layer of chorion trophoblast cells (yellow) forms the second epithelial layer of the fetal membranes and is critical for immune homeostasis. The fetal chorion layer is directly connected to the maternal decidua layer (green) forming the feto-maternal interface of the membranes. Resident immune cells predominantly live in the decidua layer but can migrate into the chorion and amnion layers if stimulated.