Placenta and Reproductive Medicine

REVIEW ARTICLE

Investigating the global research landscape, barriers, and facilitators of scientific productivity in fetal membrane research

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Abstract

Fetal membrane (FM; amniochorion) studies are an essential field of research for understanding their role during pregnancy maintenance and mechanisms associated with parturition. This paper determined the landscape and characteristics of published FM research, identified socioeconomic indicators related to FM research productivity and impact and proposed major studies using this tissue. A review of the literature about FM from 2000 to 2021 was performed using the Scopus database. Bibliometric information was obtained from Scopus, statistical analysis was conducted using GraphPad Prism, and network visualization was conducted using VOSviewer software. A total of 1131 articles were analyzed in this study. The number of publications in the past decade increased linearly. Most of the research outputs were produced by researchers from the United States of America (USA), followed by China and Australia. The most productive institutions were primarily from the USA and Australia. The current research trends based on keywords analysis were related to FM weakening, such as aging, bacterial infections and inflammations, biomechanical weakening, exosomes, immunomodulation, and sterile inflammation. Gross domestic product and the number of collaborations with other countries were the most significantly correlated indicators with increased scientific productivity and impact in FM research. We emphasize the need to increase investment and support to researchers doing FM studies, especially in developing countries. These will contribute to advancing this field and may help provide more evidence to control and manage pregnancy complications, such as preterm premature rupture of membranes and preterm birth.

Key words: amnion, bibliometrics, chorion, obstetrics, pregnancy, preterm birth

INTRODUCTION

The human fetal membrane (FM) represents the tissue that overlays the amniotic cavity.[1] It comprises two layers of cells, the amnion cells and the chorion trophoblast cells[2,3] (Figure 1). Both layers are connected by an extracellular matrix (ECM), rich in various collagens and mesenchymal cells, creating a barrier capable of maintaining and protecting the fetus during the gestational period.[1,4] The two cell layers are attached to the ECM through a Type IV collagen-rich basement membrane. The end of pregnancy is characterized by a physiological mechanism of labor resulting from complex events involving the endocrine and immune systems.[5] During parturition, the FM undergoes a process of weakening and rupture, accompanied by a pro-inflammatory response.[1,4]

Despite the worldwide research efforts in understanding

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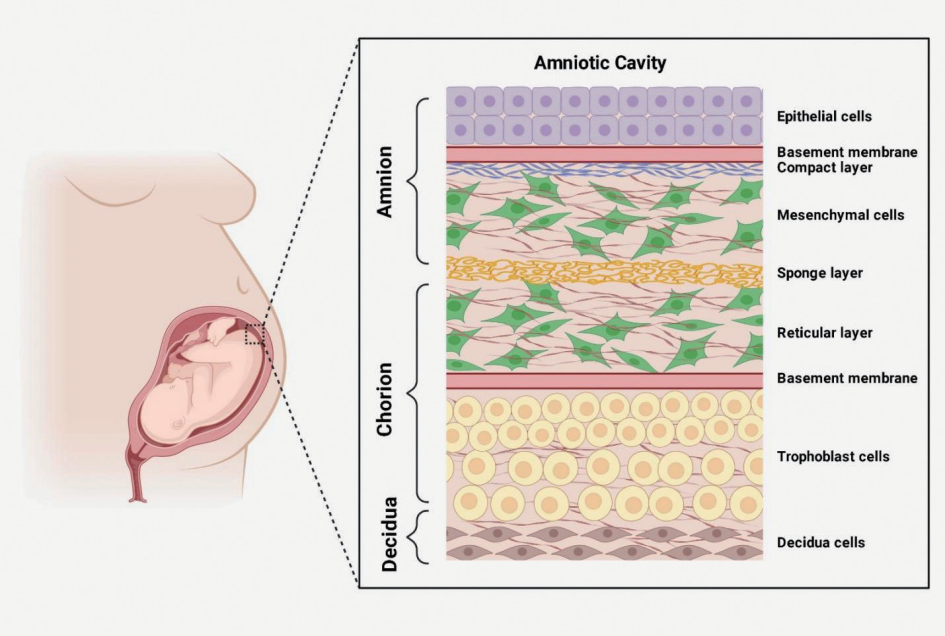

Figure 1. Schematic structure of the fetal membrane. The amnion represents the innermost layer, composed of epithelial cells (purple), which are connected to the basement membrane (red strips) and compact layer (red) and amnion mesenchymal cells (green). The outer layer, called the chorion layer, is composed of the reticular layer (green) and chorion trophoblast cells.

preterm birth (PTB) and preterm premature rupture of membranes (pPROM), the causes, risk factors, pathways, and effective management remain unclear. A possible explanation is the complexity and heterogeneity of the pathophysiology involving PTB and pPROM.[6–8] PTB can be caused by multiple etiologies, including cervicovaginal infection that can lead to intraamniotic infection, sterile inflammation, autoimmune diseases, cervical insufficiency, placental abruption, multifetal pregnancy, and preeclampsia.[8,9] Furthermore, most studies related to spontaneous PTB (SPTB) tend to investigate the maternal tissues, while the role of the FM in SPTB has been emerging in the past decades.

The limited number of studies focused on FM research can be attributed to several challenges. Obtaining FM tissues during pregnancy presents practical difficulties, primarily feasible only in cases of preterm delivery. However, preterm deliveries are frequently accompanied by complications like infection, sterile inflammation, and preeclampsia. These complications can introduce confounding variables that affect the outcomes of FM studies. Additionally, acquiring intact FM tissues for research purposes proves challenging, often requiring samples from term pregnancies that are not in labor, which are typically accessible during elective Cesarean deliveries.[10] Furthermore, existing animal models used for FM research lack the accurate histological resemblance and rupture physiology to human FM tissues.[11]

There is still no systematic analysis of worldwide research trends in FMs. Bibliometric analysis is a review methodology that can identify authors, researchers, and collaborations related to a specific topic in a quantitative manner.[12] It can be a valuable tool to help the scientific community identify possible gaps and trends in the FM field. This method has been applied in research in obstetrics and gynecology,[13,14] cervical remodeling during pregnancy,[15] and preeclampsia.[16] Since FMs are functionally highly relevant tissues and their role in pregnancy, parturition at term and preterm are rapidly emerging. This paper determined the landscape and characteristics of published FM research. This study also proposed future research areas to understand the contribution of FM in pregnancy and parturition. We also identified socioeconomic indicators associated with FM research productivity and impact.

METHODS

A systematic review of the literature was performed using the Scopus database. Scopus is one of the largest databases of research articles. The search strategy can be found in the supplementary materials. All electronic searches were performed from February to March 2022. All FM-related articles from 2000 to 2021 were included in the study. The following information was obtained for each article: authors, year of publication, title, journal, institution, country, title, keywords, citation frequency, source of funding, and subject area of the FM studies. These were used to investigate FM research's knowledge domain and development trends worldwide.

Four publication indicators were used to evaluate the publication performance of countries and institutions: total number of paper (TP), total number of citations (TC) until the time of database search in Scopus, citations per

paper (TP/TC, CPP) and number of papers with citation number ≥ H (*h*-index).

Spearman's rank-order correlation determined correlations between country-specific characteristics with the different bibliometric indices. The socioeconomic indicators were obtained from the World Bank. The Spearman's correlation coefficient (ρ) was considered significant if the *P*-value was less than 0.05. This statistical analysis was done using GraphPad Prism software (version 8.0.1, GraphPad Software, San Diego, CA). The visualization of collaboration networks of countries and keywords used for FM research was conducted using VOSviewer (version 1.6.16, Leiden University, Leiden, Netherlands).[17]

RESULTS

Trends over time of FM publications

We obtained 1131 articles related to the FM in the Scopus database from 2000 to 2021. We observed an increase in the research outputs on FM starting in 2010, which peaked in 2020 (Figure 2).

FM publications by country

The most productive countries in FM research were the USA with 368 papers, which received 10, 154 citations, followed by China with 116 publications and 1176 citations, and Australia with 108 publications and 3046 citations. Canada had the highest citations per publication at 36.94, while the USA had the highest *h*-index at 56 (Table 1).

Figure 3 shows the inter-country collaboration for FM research. We observed a strong linkage between the most productive countries, including the USA, China, and Canada. These countries also had the highest number of FM articles with international co-authorship.

FM publications by institutions

The most productive institutions were the University of Texas Medical Branch at Galveston, USA, with 57 papers and 1353 citations, followed by the University of Melbourne, Australia, with 52 papers and 1419 citations, and Mercy Hospital for Women, Australia, with 43 papers and 1197 citations (Table 2). These institutions were also from the most productive countries in FM research.

FM publications by categories and journals

Most of the published articles on FM research were classified in Scopus in the field of Medicine (72.59%), Biochemistry, Genetics, and Molecular Biology (42.53%), and Agricultural and Biological Sciences (7.96%). Interestingly, there were also studies classified as Engineering (4.86%), Pharmacology, Toxicology, Pharmaceutics (2.65%), and Materials Science (2.03%) (Supplementary Figure 1).

The most productive journal in FM research was *Placenta*, with 85 publications and 2543 citations (Table 3). On the other hand, the most-cited journal was the *American Journal of Obstetrics and Gynecology*, with 2835 total citations and an *h*-index of 35. The *Journal of Clinical Endocrinology and Metabolism* had the highest citations per paper (TC/TP) at 51.53.

Research funding for FM research

During the 21st century, 159 funding agencies supported FM research (Supplementary Figure 2). The Eunice Kennedy Shriver National Institute of Child Health and Human Development in the USA provided funding for 128 FM research outputs. This accounts for 11.31% of the total FM research outputs in the 21st century. The National Institutes of Health supported 113 research outputs, the US Department of Health and Human Services funded 39 research outputs (3.45%), the UK National Health and Medical Research Council funded 36 research outputs (3.18%), and the National Natural Science Foundation of China supported 33 research outputs (2.92%).

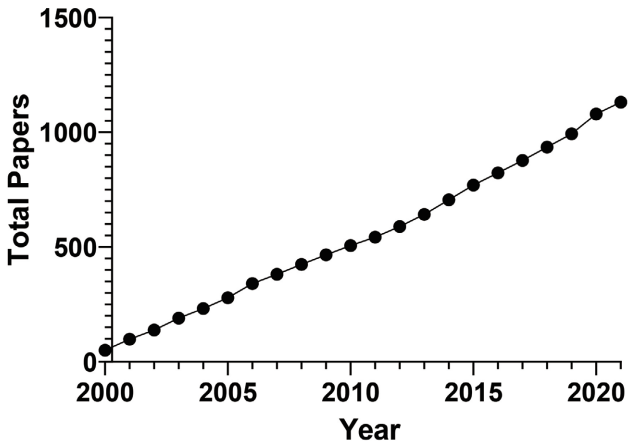

Figure 2. Annual number of research outputs in fetal membrane research from 2000 to 2021.

Table 1: Most productive and influential countries in fetal membrane research

Country	TP	TC	CPP	*h*-index
United States	368	10154	27.59	56
China	116	1176	10.14	19
Australia	108	3046	28.20	29
United Kingdom	90	4105	45.61	32
Japan	71	1519	21.39	20
Canada	49	1810	36.94	24
Brazil	40	507	12.68	13
Germany	38	928	24.42	18
France	35	649	18.54	15
Italy	35	716	20.46	16
Switzerland	35	968	27.66	19
Turkey	35	217	6.20	7

TP: total number of papers; TC: total number of citations; CPP: citations per paper

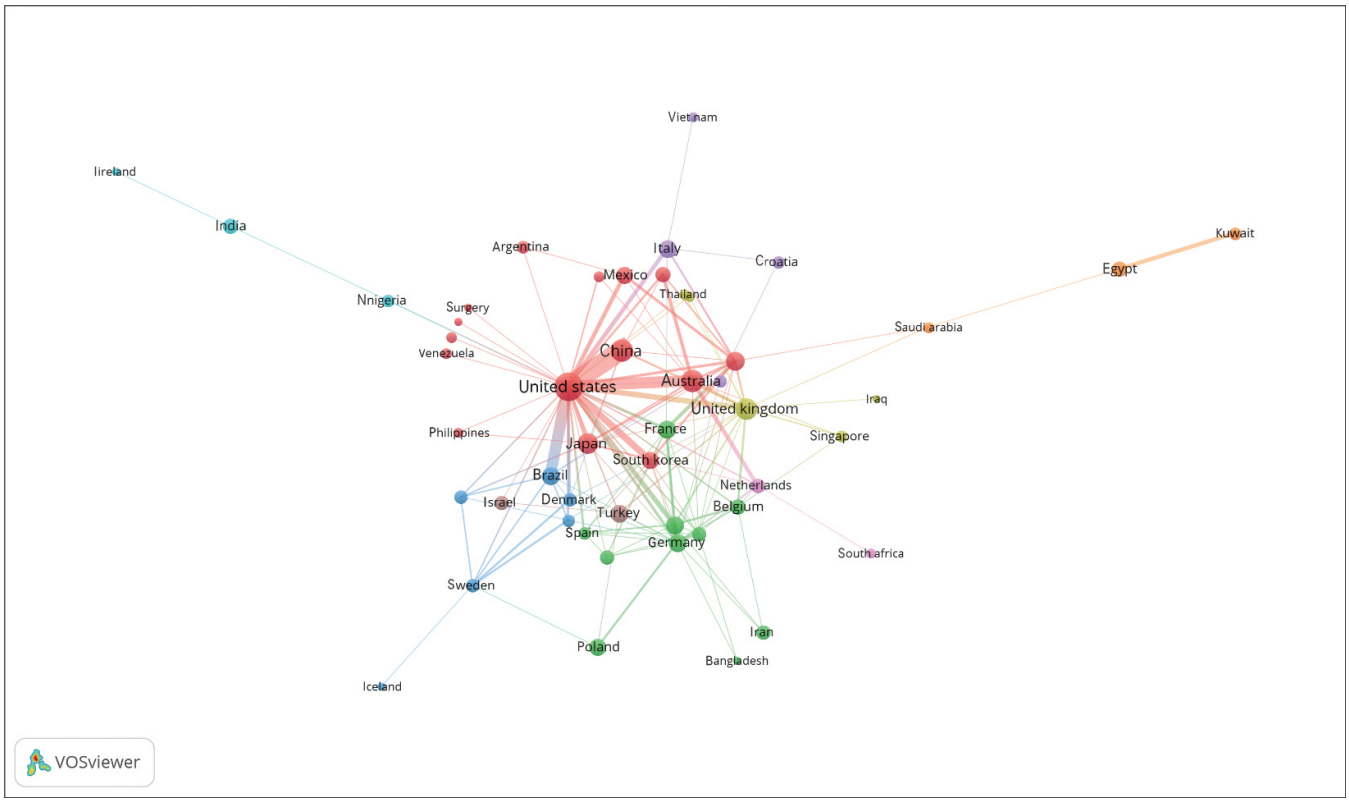

Figure 3. Network visualization of international collaboration for fetal membrane research. The size of the circle is proportional to the number of collaborations in the cooperation network. The thickness of the lines indicates the link strength between countries.

Table 2: Most productive and influential institutions in fetal membrane research

Institution	Location	TP	TC	CPP	*h*-index
University of Texas Medical Branch at Galveston	USA	57	1353	23.74	23
University of Melbourne	Australia	52	1419	27.29	19
Mercy Hospital for Women	Australia	43	1197	27.84	17
Monash University	Australia	29	1065	36.72	17
Case Western Reserve University	USA	27	1084	40.15	17
Instituto Nacional de Perinatologia	Mexico	24	785	32.71	15
Hudson Institute of Medical Research	Australia	23	972	42.26	16
Yale School of Medicine	USA	22	701	31.86	15
University of Toronto	Canada	21	915	43.57	15
Perinatal Research Center	USA	20	878	43.90	15
Imperial College London	UK	20	957	47.85	16
Oregon Health & Science University	USA	20	352	17.60	10
UniversitatsSpital Zurich	Switzerland	20	454	22.70	14
Shanghai Jiao Tong University	China	20	213	10.65	9

TP: total number of papers; TC: total number of citations; CPP: citations per paper

FM research trends

Network visualization using VOSViewer was performed to determine the evolution of keywords used in FM research from 2000 to 2021 (Figure 4). During the early years of the 21st century, the keywords used include tissues and cells involved in pregnancy and parturition, such as cervix, uterus, trophoblast, and leukocytes. It also had keywords about the mechanism of labor, such as cytokines, interleukin (IL)-1β, lipopolysaccharide, MMP-9, and prostaglandin. From 2010 to 2015, the most common keywords include biomechanics, inflammation, oxidative stress, thrombin, and tumor necrosis factor-α. The most recent keywords in FM research include other compounds and cytokines involved in FM weakening, such as α-lipoic acid and granulocyte-macrophage colony-stimulating factor. Some current keywords were related

Table 3: Most productive and influential journals that published fetal membrane research

Journal	TP	TC	CPP	*h*-index
Placenta	85	2543	29.92	32
American Journal of Obstetrics and Gynecology	57	2853	50.05	35
Biology of Reproduction	40	1984	49.60	24
Reproductive Sciences	36	579	16.08	14
Molecular Human Reproduction	31	1571	50.68	18
American Journal of Reproductive Immunology	28	482	17.21	13
Plos One	23	651	28.30	14
Journal of Clinical Endocrinology and Metabolism	19	979	51.53	16
Journal of Maternal Fetal and Neonatal Medicine	19	160	8.42	6
Journal of the Society for Gynecologic Investigation	16	479	29.94	12

TP: total number of papers; TC: total number of citations; CPP: citations per paper

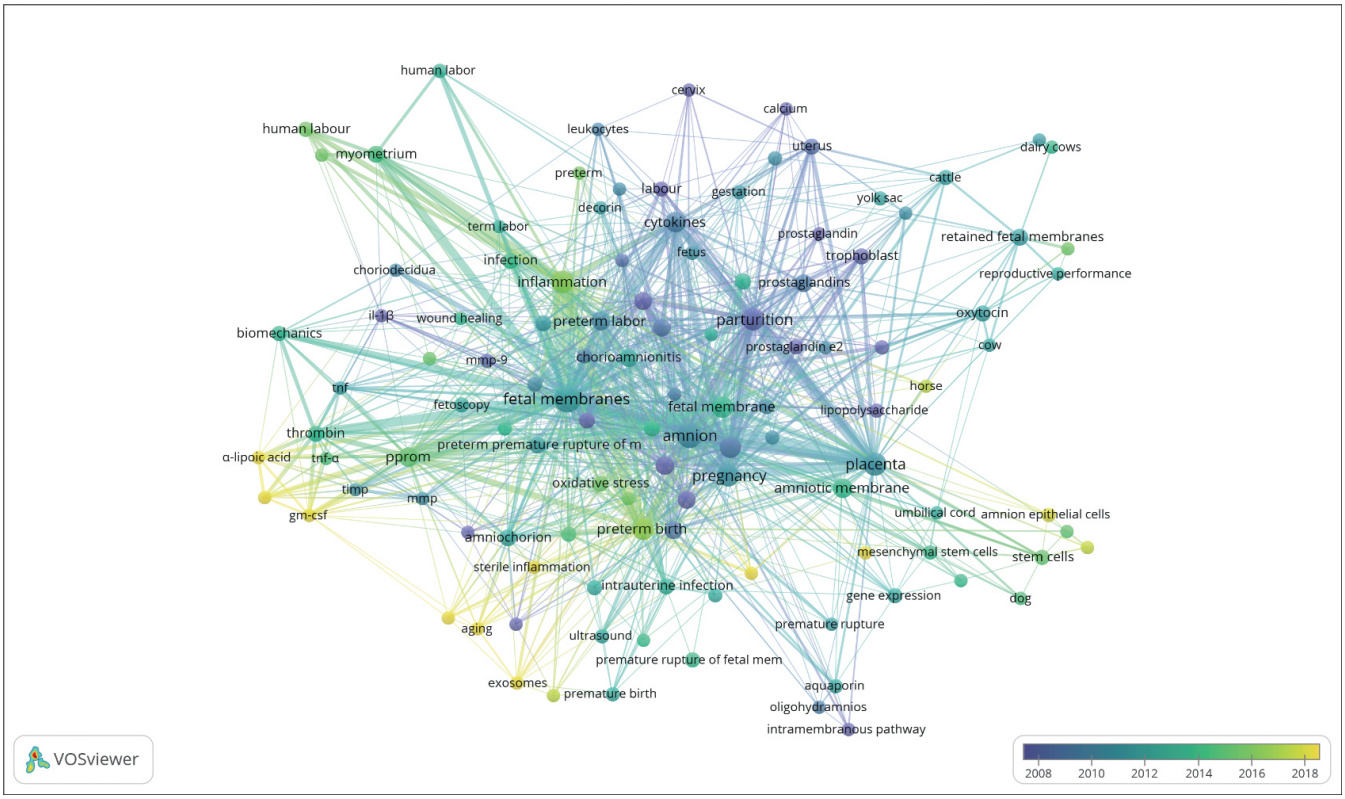

Figure 4. Network visualization of author keywords linked to fetal membrane research.

to new concepts associated with FM weakening, such as aging, bacteria, biomechanical weakening, exosomes, immunomodulation, and sterile inflammation.

Country-specific socioeconomic indicators associated with scientific productivity in FM research

Correlation analysis was performed to determine the socioeconomic indicators associated with increased scientific productivity in FM research (Table 4). We observed that the gross domestic product (GDP) (TP: $r = 0.7987$; TC: $r = 0.7559$; CPP: $r = 0.5112$; *h*-index: $r = 0.7695$) and the number of collaborations with other countries (TP: $r = 0.8016$; TC: $r = 0.7879$; CPP: $r = 0.4996$; *h*-index: $r = 0.7848$) were the most significantly correlated with increased scientific productivity and research impact. Other socioeconomic indicators such as the country's GDP per capita, research and development (R&D) expenditure, physicians per million people, and researchers in R&D per million people also positively correlated with increased research outputs in FM research.

DISCUSSION

This study observed a linear increase in published research on FMs. From 2000 to the end of 2021, there were 1131

Table 4: Correlation analysis between socioeconomic indicators and scientific productivity and impact of fetal membrane research

Country-specific characteristics	Bibliometric indices	*r*	*P*-value
GDP	TP	0.7987	< 0.001
	TC	0.7559	< 0.001
	CPP	0.5112	< 0.001
	h-index	0.7695	< 0.001
GDP per capita	TP	0.3885	0.002
	TC	0.527	< 0.001
	CPP	0.6415	< 0.001
	h-index	0.4618	< 0.001
R&D expenditure (% GDP)	TP	0.5116	< 0.001
	TC	0.569	< 0.001
	CPP	0.4384	< 0.001
	h-index	0.5326	< 0.001
Physicians (per million people)	TP	0.2932	0.035
	TC	0.4077	< 0.001
	CPP	0.5276	< 0.001
	h-index	0.3341	< 0.001
Researcher in R&D (per million people)	TP	0.4513	0.001
	TC	0.5459	< 0.001
	CPP	0.5639	< 0.001
	h-index	0.4973	< 0.001
International collaborations	TP	0.8016	< 0.001
	TC	0.7879	< 0.001
	CPP	0.4996	< 0.001
	h-index	0.7848	< 0.001

R&D: research and development; TP: total number of papers; TC: total number of citations; CPP: citations per paper

articles. This trend paralleled the general increase in the research publications in obstetrics and gynecology.[13] This study showed that the most productive institutions in FM research were from developed countries. The USA still has higher proportions of publications and elite researchers in the past years.[18] There was limited evidence and information from developing countries, especially countries with higher adverse pregnancy outcomes. This regional imbalance in knowledge generation will hinder our understanding of the pathologic conditions involving FMs (*i.e.*, chorioamnionitis, intraamniotic infection, and pPROM) associated with adverse pregnancy outcomes. Our study showed that the country's GDP per capita, R&D expenditure, and the number of researchers were correlated with scientific productivity in FM research. This result agrees with previous bibliometric analyses that reported that financial support and human resources are necessary factors linked to research productivity.[19–21] Therefore, we emphasize the need for financial support to improve FM research in developing countries. This financial support should focus on research facilities and researchers' training and capacity building.

Academic and scientific societies such as the American Society for Reproductive Immunology, Fetal Membrane Society, International Federation of Placenta Associations, Preterm Birth International Collaborative Inc., and Society for Reproductive Investigation also play a considerable role in advancing our knowledge on the role of FM in pregnancy. These societies support investigative research in FM and are usually more common in developed countries than in developing countries. Hence, strengthening the presence of these academic societies in developing countries may increase FM research and promote advancements in the field.

This study also showed that the most productive countries in FM research have more international collaborations. This result emphasizes the role of partnerships in increasing the research outputs and scientific impact of FM research in a country.[22] Previous bibliometric analyses also showed that the research groups and institutions open to collaboration have higher research outputs and scientific impact.[19,21] Furthermore, collaborations promote better research quality, broader connections for future works, and increased knowledge.[23,24] Therefore, researchers from developing countries should consider forming partnerships and collaborations with researchers in productive countries in FM research.

The most influential journals that published articles related to FM research were written in English. Most of the top journals that published FM research were specialty journals related to obstetrics, gynecology, and reproductive sciences. These journals also have reasonable impact factors and are indexed in reputable databases. This result shows that FM researchers prefer publishing in specialty journals targeting reproductive science researchers. Previous studies showed that the relevance of the research field, impact factors, and indexation are the primary determinants of the submission choice of seasoned authors for publishing their research results.[25,26] The FM can be a helpful research model for understanding its structure, function, and biomechanics, enabling a relevant comprehension of term and preterm parturition. Furthermore, it can provide a set of immune and endocrine functions and a stem cell source, making the FM a vital model to study. Based on the most common keywords used in the recently published articles in the FM, the current trends and potential direction of FM research were on aging, bacteria, biomechanical weakening, exosomes, immunomodulation, and sterile inflammation. These keywords inform us of the current trends and potential areas of investigation in FM research. The role of aging and senescence in FM weakening and rupture have been extensively studied. Senescent cells, due to changes in their phenotypes, can produce a set of biomarkers,[27] such as cytokines, chemokines, and growth factors, forming the senescence-associated secretory phenotype, increasing the pro-inflammatory profile and leading to labor.[28] The aging of the FM, related to the senescence process, has been associated with labor induction signaling.[29]

The role of biomechanical weakening of the FMs has been previously studied.[30,31] Different research groups a combined biochemical, histologic, and bioengineering approaches to understanding the physiologic mechanisms involved in FM weakening and rupture. These *ex vivo* studies using human FM tissues studies demonstrated that cytokines, such as granulocyte-macrophage colony-stimulating factor, thrombin, and tumor necrosis factor-alpha, promote inflammation and collagen degradation in the FMs.[31–35]

Extracellular vesicles (EVs), including exosomes and microvesicles, have been shown to function in paracrine signaling to promote fetal and maternal inflammation in pregnancy and parturition.[36–39] *In vivo* studies in animal models, *in vitro* studies using monoculture and organ-on-a-chip devices (OOC), and clinical studies on the functional role of different EVs from gestational tissues and cells, trafficking in the feto-maternal interface, and mechanisms of biogenesis will advance the knowledge in the field, including the application of EVs as a diagnostic or prognostic biomarker in pregnancy.[40–43]

Lastly, *in vitro*, *in vivo*, and clinical studies on the role of sterile inflammation and infection in FMs also increased in the past few years.[44–46] Damage-associated molecular patterns, such as uric acid, high-mobility group box 1 (HMGB1), IL-1, and cell-free fetal DNA, were implicated in inflammation in FM.[47] Moreover, oxidative stress can promote sterile inflammation and increase inflammatory markers, such as Nrf2 and HMGB1, and an alarmin.[44–46] The response of FM cells against some species, such as genital mycoplasmas,[48,49] *Streptococcus agalactiae*,[50] and *Escherichia coli*[51] was also studied since intra-amniotic infection and inflammation are closely related to PTB and a critical matter to the obstetrics field.

Aside from these current research trends, we propose new models and systems to study the role of FM in pregnancy and parturition. Microfluidic organs-on-a-chip that mimic the FM have recently gained much interest and attention.[52–54] These devices mimic the physiologic microenvironment of tissues and organs. The amnion membrane OOC and feto-maternal interface OOC (FMi-OOC), which mimic the different layers of the FMs (*i.e.*, amnion epithelial, amnion mesenchymal, chorion trophoblast, and decidual cells), have helped study infection, inflammation, and EV-mediated signaling in the different FM cellular layers. FMi-OOC has also been helpful in pharmacokinetic studies (*e.g.*, rosuvastatin and pravastatin). Statins permeated the maternal–fetal cell layers of the FMi-OOC and demonstrated cell and time-specific statin metabolites from various cell types without causing any cytotoxicity in the FM cells.[55,56] OOC devices were also used in studying FM cellular response to environmental toxins, such as cadmium. Recently, studies using 3D culture of FM cells are also increasing to optimize therapeutic techniques for PTB.[57,58] These newer models will improve our understanding of FM biology and its role in pregnancy and parturition.

The utility of FMs was well recognized outside the field of reproduction and perinatal medicine.[59,60] Stem cell properties of this tissue are useful to investigators and industries in regenerative medicine. Multipotent fetal stem cells have gained significant attention in the realm of reproductive biology research and clinical applications, particularly in the context of tissue repair and regeneration. Utilizing FMs as a source of these stem cells carries distinct advantages, primarily due to the absence of ethical concerns and stringent legal limitations often associated with other sources. FMs hold the potential for banking these multipotent stem cells for later autologous utilization. This approach offers the prospect of harnessing these cells for therapeutic purposes in an individual's future, contributing to personalized medicine and long-term health management.[60,61] The articles published in this area are not considered for this review.

CONCLUSION

FMs are traditionally ignored tissue by perinatal and

reproductive biologists for research purposes to understand pregnancy and parturition. FM studies were ignored with the notion that FMs are a mere extension of the placenta, and exclusive studies using FM are necessary. This has led to misclassification of this tissue, lack of funding for its research, and produced a plethora of data using placental cells that were wrongfully denoted as FM data. A handful of investigators have helped steer this field of research in the past couple of decades, and their attempts have been fruitful, as seen in this bibliometric analysis. This bibliometric analysis showed a linear increase in FM research worldwide. Most significant research outputs were conducted by institutions from developed countries, with the USA as the most productive country in FM research. Countries from South America and Africa lacked substantial scientific outputs in the FM field. This study showed that economic status, research funding, and international collaborations are significantly associated with scientific productivity in FM research. We emphasize the need to increase investment and support to researchers doing FM studies, especially in developing countries. These will contribute to advancing this field and may help provide more evidence to control and manage pregnancy complications, such as pPROM and PTB.

DECLARATIONS

Supplementary materials

Supplementary materials mentioned in this article are online available at the journal's official site only.

Author contributions

de C. Silva M, Bento GFC, Troitino VC, and Tantengco OAG performed the systematic review, analyzed the data, and wrote the manuscript. Menon R helped in analyzing and interpreting the data and writing the manuscript. All authors read and approved the final manuscript.

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Consent to participate

Not applicable

Ethics approval

Not applicable.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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