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REVIEW ARTICLE

Chorion and amnion/chorion membranes in oral and periodontal surgery: A systematic review

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Abstract

The aim of this study was to perform a systematic review on the clinical applications where chorion membrane (CM) and amnion/chorion membrane (ACM) were used for oral tissue regeneration procedures. Selection of articles was carried out by two evaluators in Pubmed and Scopus databases, and Outcomes (PICO) method was used to select the relevant articles. Clinical studies reporting the use of CM or ACM for oral soft and hard tissue regeneration were included. The research involved 21 studies conducted on 375 human patients. Seven clinical applications of CM and ACM in oral and periodontal surgery were identified: gingival recession treatment, intrabony and furcation defect treatment, alveolar ridge preservation, keratinized gum width augmentation around dental implants, maxillary sinus membrane repair, and large bone defect reconstruction. CM and ACM were compared to negative controls (conventional surgeries without membrane) or to the following materials: collagen membranes, dense polytetrafluoroethylene membranes, platelet-rich fibrin membranes, amnion membranes, and to a bone substitute. Several studies support the use of CM and ACM as an efficient alternative to current techniques for periodontal and oral soft tissue regeneration procedures. However, further studies are necessary to increase the level of evidence and especially to demonstrate their role for bone regeneration.

KEYWORDS
amniochorion, chorion, fetal membrane, guided bone regeneration, guided tissue regeneration, oral surgery, periodontal surgery

1 | INTRODUCTION

The human placenta is composed of two membranes: the amniotic membrane, which is in contact with the fetus and the outer chorionic membrane (CM). One of the main properties of these fetal membranes is their elastic strength that allows the amniotic cavity to be maintained in the uterus during fetal growth. In addition, they secrete anti-inflammatory cytokines, chemokines, and growth factors such as Platelet-Derived Growth Factor AA (PDGF-AA) and Vascular endothelial growth factor (VEGF).[1,2] Amniotic membranes and CM exert anti-inflammatory,[3,4] angiogenic,[5-7] antifibrotic,[8,9] and antimicrobial effects.[10,11] They also possess low immunogenicity and improve epithelialization.[8,12,13] The placenta is a simple source of biological membranes without major restrictions as it is considered a biological waste. With an estimated birth rate (annual number of births/total population) of 18.3 worldwide in 2019, this is a readily available biomaterial.[14]

These fetal membranes have been used in medicine since the 1910s for skin wound care and ophthalmology.[15-19] Today clinical applications have expanded[20]: they can be used in dermatology[21] or plastic surgery[22] as a skin substitute to treat burns,[23,24] diabetic foot ulcers,[25,26] or venous leg ulcers.[27,28] These membranes are also used

in orthopedic surgery, in particular for repairing tendons and ligaments, to treat joints and cartilage diseases or prevent scars formation.[29,30] They are used in gynecology[31] and urology.[32,33] Fetal membrane and their derivates are also considered as attractive biological scaffolds for tissue engineering.[34-36]

There is also a growing interest in the use of placental membranes allografts as an alternative to conventional membranes in oral surgery.[37-39] Indeed, both absorbable and nonabsorbable membranes currently used to regenerate oral soft and hard tissues have some limitations.[40,41] Nonresorbable membranes have often been associated with oral exposure through the soft tissue and a second surgical intervention is always needed for membrane removal. Resorbable membranes have low-mechanical strength and their degradation can induce a strong inflammatory response during the post-operative healing phase. They also lack biological properties, thereby justifying search for alternatives.[42] Placental membranes are thus promising bioactive membranes for oral guided tissue regeneration.[43-46] We previously investigated the usefulness of amniotic membrane in the field of oral surgery: periodontal surgery, prosthodontics and peri-implant surgery, cleft palate surgery, and tumoral reconstruction were identified as the main clinical indications.[47] Another study investigated the different properties of the amnion and CM and their potential uses in periodontology. Fourteen clinical applications were identified. Most of them used the amnion alone, whereas only three studies used the CM or the CM in combination with the amnion (ACM).[12] However, the amniotic membrane is thin which makes its manipulation difficult. To overcome this limitation, the use of CM, which is four to five times thicker than amnion, or the CM in conjunction with amnion (ACM) could be an interesting alternative. Besides, the antibacterial effects of the chorion are superior to those of the amnion; it plays a key role in protecting the fetus from infection.[48] The CM or ACM contain four to five times more growth factors and cytokines than the equal surface area amnion,[49] thereby further promoting wound healing.[1]

The mechanical and biological properties of CM and ACM thus provide new biological membrane options in oral and periodontal surgery. However, there is no study that summarizes CM and ACM clinical applications and their efficacy to regenerate oral soft and hard tissues. The purpose of this study was thus to perform a systematic review on the clinical use of CM and ACM in oral and periodontal surgery.

2 | MATERIALS AND METHODS

This review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA),[50] and has been registered in PROSPERO database (N° CRD42020187215).

2.1 | Focused question

The search strategy was developed based on the PICO reporting system. The following focused question was defined: "In which clinical indications have chorion and amnion/chorion membranes (ACM) been shown effective for soft or hard tissues repair in the field of oral surgery?"

2.2 | PICO question

P (patients): patients who required an oral surgery procedure.

I (intervention): the use of CM or ACM, combined or not to a biomaterial.

C (comparison): defined procedures without the use of CM or ACM.

O (outcomes): oral soft or hard tissue repair and regeneration in oral area.

2.3 | Search strategy

An electronic search of the MEDLINE—Pubmed database and the Scopus database was carried out. We searched for articles published in English up to and including July 2019. The following search combination was used: (chorion* or amnion/chorion or "chorionic membrane") and ("guided bone regeneration" or "bone regeneration" or "guided tissue regeneration" or "oral surgery" or "tissue regeneration" or "periodont*" or "tongue" or "maxillary" or "jaw" or "gum" or "oral mucosa" or "oral cavity"). Additional articles were also added after manually screening the list of references of all publications selected by the search.

2.4 | Selection criteria

Studies published in English and conducted on human subjects were included. Only studies analyzing the effectiveness of CM or ACM in oral tissue reconstruction were considered. Prospective (randomized controlled, nonrandomized controlled, cohort) and retrospective studies (controlled, case control, single cohort) and case series were included. in vitro studies, preclinical studies, studies based on the use of CM or ACM cells without their matrix and case reports were excluded.

2.5 | Screening of studies and data collection

Two independent reviewers (M.F. and S.G.) performed the article selection and data extraction. The title and the abstract were screened in the first time according to the question: "in which clinical indications have CM or ACM been shown effective for soft or hard tissues repair in the field of oral surgery?." Full-text articles were then assessed, and finally, the article selection was made. In case of disagreement between the reviewers, articles were discussed to decide the final outcome. Structured tables were generated and used to collect directly relevant data from selected papers. The data extracted from the reports were general

characteristics (authors and year of publication), type of membrane (CM or ACM), level of evidence, number of patients involved, total duration of the study, the clinical applications, treatment procedures, evaluation criteria, and efficacy of the membranes. The preservation methods as well as the use of both membranes were also recorded: these included the processing and preservation techniques of ACM or CM, the side applied against the defect, the membrane fixation using suture, and if the membrane was left exposed to the oral cavity or not. For missing information in the selected articles, the authors were contacted by email to complete the data. The level of evidence of the included studies was assessed using the National Health and Medical Research classification.[51]

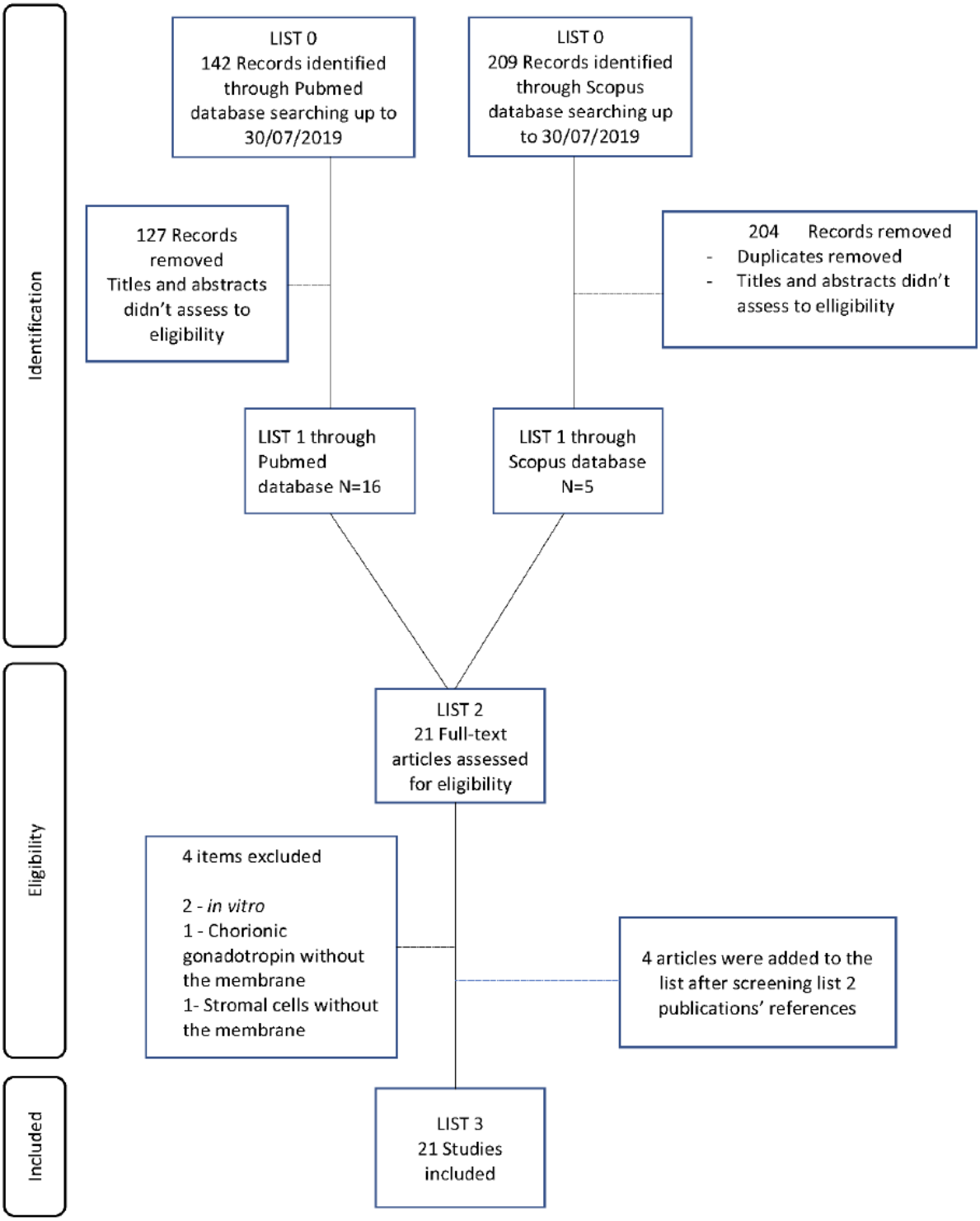

FIGURE 1 Flow diagram of the screened publications

2.6 | Analysis of the data

Data analysis was performed in a descriptive way, since the information obtained did not enable meta-analyses.

3 | RESULTS

3.1 | Search outcomes

In total, the search generated 142 potentially relevant articles from Pubmed and 209 from the Scopus database. After reading titles and abstracts, 16 articles from Pubmed database and 5 from Scopus were retained for further investigation. Entire publications have been read and 17 eligible articles were selected. Four articles were added to the list after screening the references of these 17 publications. Finally, 21 articles met the eligibility criteria and were included in this systematic review. The selection process is shown in Figure 1. All included articles have been published from 2013 and 11 studies were performed in India. Based on the level of evidence, most of the studies were randomized clinical trials (n = 13) and eight were case series. This selection was separated accordingly into three main areas: periodontal surgery,[3,37,52-64] implant and preimplant surgery[65-69] and bone reconstruction following tumor resection.[70]

3.2 | Methods of CM/ACM preservation and use

In 11 studies, patients had a CM allograft[3,52-56,58,60-62,66] whereas in the other 10 studies an ACM allograft was performed.[37,57,59,63-65,67-70] Membranes were freeze-dried in seven studies,[3,52,56,58,60-62] decellularized then freeze-dried in one study,[70] de-epithelialized and dehydrated by the Purion process in nine studies,[37,57,59,63-65,67-69] and just dehydrated in two studies.[53,55] In two publications, the preservation methods were not mentioned.[54,66] All the membranes were then sterilized. The membranes supplied by the Tata Memorial Hospital tissue bank were irradiated with γ radiation,[3,52-56,58,60-62,66] Kakabadze et al. used γ rays at a dose of 15 kGy,[70] and the BioXclude membranes were sterilized by γ rays or irradiated by electron beams at a dose of approximately 17.5 kGy.[37,57,59,63-65,67-69] The membranes were used in monolayer in all studies, but some authors specified that if the membrane folds on itself together, it was not unfolded.[37]

None of the selected articles mentioned which side of the membrane was applied in contact with the defect. However, some authors were contacted via email and the mentioned that they placed no importance on the side during implantation.[3,53,56,58,60-62,64,67] In only four studies the membrane was sutured to be stabilized,[55,66,68,70] otherwise it was just applied to the surgical site.[3,37,52-54,56-65,67,69] The membrane was left exposed voluntarily in four studies.[65-68] In most studies, the membranes were applied dried and were then rehydrated by the blood during the surgical procedure. One author rehydrated the membrane in 0.9% saline for 30 min before grafting.[70] Membrane use strategies were summarized in Table 1.

3.3 | Clinical applications

Clinical studies are summarized in Table 2.

3.3.1 | Periodontal surgery

Use of CM or ACM for treatment of gingival recessions

Seven studies reported the use of CM[52-56,58] and ACM[57] associated with a coronally advanced flap technique to perform root coverage of gingival recessions. Five of them were clinical trials, which compared CM to amniotic membranes[52-55] or to platelet-rich fibrin (PRF) membranes.[56]

One study reported a significant improvement of all investigated parameters using CM compared to PRF membrane, except for the recession width where the difference was not significant between both groups.[56] Two studies showed no significant difference in covering gingival recession using CM or the amnion.[52,54] In another study, CM was significantly better than the amnion for part of the parameters (recession width and root coverage), and there was no significant difference for the rest of parameters.[55] Chakraborthy et al. showed a significant gain of keratinized gingiva after 3 months for the CM group compared with the amnion group, whereas a significantly smaller recession width was observed in the amnion group.[53] These four studies concluded that CM showed equal or better results compared to the use of the amnion alone for gingival recession treatment. The two remaining studies were case series which reported significant improvement of the gingival recession using CM.[57,58]

Use of CM or ACM for intrabony defect regeneration

The use of CM and ACM to treat periodontal pockets was reported in six studies, including five randomized trials. Temraz et al. compared the implantation of ACM alone to a bone substitute (DBM putty) without a membrane, and no significant difference was observed between both groups for clinical and radiological parameters after 6 months.[59] In three studies Kothiwale et al. compared CM to a control group (open flap debridement without membranes) and they observed significantly superior results for all investigated parameters using CM.[3,60,62] In one study, the CM was used to cover two types of bone substitutes. The study criteria were significantly improved in both groups.[61] The last study was a case series where ACM was used in combination with a freeze-dried cortical bone allograft. An improvement of pocket depth and clinical attachment level was recorded in this study.[37]

Use of ACM for furcation defect treatment

ACM was used in two studies to treat furcation lesions. In Taalab et al., randomized clinical trial study, ACM was associated with an alloplastic bone graft and was compared to a collagen membrane in combination with the same bone graft. ACM showed significantly better results at 180 days concerning clinical attachment, quantity of keratinized gum and furcation components. There was no difference between the groups for pocket depth.[63] The other study was a case

TABLE 1 Preservation methods and uses strategies of amniochorionic membrane (ACM) and chorionic membrane (CM). N/A not applicable

Author/year	CM/ACM	Preservation method	Flap technique	Suture of the membrane	Exposition of the membrane in the oral cavity
Chakraborthy et al. 2015	CM (Tata memorial hospital TB)	Dehydrated	Split-thickness flap	No	Nonexposed
Gupta et al. 2018	CM (Tata memorial hospital TB)	Freeze-dried	Split-thickness flap	No	Nonexposed
Chopra et al. 2019	CM (Tata memorial hospital TB)	Dehydrated	Split-thickness flap	Yes	Nonexposed
Dandekar et al. 2019	CM (Tata memorial hospital TB)	Freeze-dried	Split-thickness flap	No	Nonexposed
Pundir et al. 2015	CM (Tata memorial hospital TB)	Not specified	Split-thickness flap	No	Nonexposed
Nevins et al. 2016	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Split-thickness flap	No	Nonexposed
Esteves et al. 2015	CM (Tata memorial hospital TB)	Freeze-dried	Split-thickness flap	No	Nonexposed
Temraz et al. 2019	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Full thickness flap	No	Nonexposed
Kothiwale et al. 2019	CM (Tata memorial hospital TB)	Freeze-dried	Full thickness flap (Kirkland)	No	Nonexposed
Kothiwale et al. 2015	CM (Tata memorial hospital TB)	Freeze-dried	Full thickness flap	No	Nonexposed
Kothiwale et al. 2018	CM (Tata memorial hospital TB)	Freeze-dried	Full thickness flap	No	Nonexposed
Kothiwale et al. 2013	CM (Tata memorial hospital TB)	Freeze-dried	Full thickness flap	No	Non exposed
Holtzclaw et al. 2013	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Full thickness flap	No	Nonexposed
Rosen et al. 2015	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Split-thickness flap	No	Nonexposed
Taalab et al. 2018	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Full thickness flap	No	Nonexposed
Hassan et al. 2017	ACM BioXclude	De-epithelialized + dehydrated (PURION)	No flap	No	Exposed
Joshi et al. 2017	CM (Tata memorial hospital TB)	Non specified	No flap	Yes	Exposed
Cullum et al. 2019	ACM BioXclude	De-epithelialized + dehydrated (PURION)	No flap	No	Exposed
De Angelis et al. 2019	ACM BioXclude	De-epithelialized + dehydrated (PURION)	Full thickness flap	Yes	Exposed
Holtzclaw et al. 2015	ACM BioXclude	De-epithelialized + dehydrated (PURION)	N/A	No	Nonexposed
Kakabadze et al. 2016	ACM	Decellularized + freeze-dried	N/A	Yes	Nonexposed

TABLE 2 Clinical applications of amniochorionic membrane (ACM) and chorionic membrane (CM)

Author/study design (NHMRC)	Using strategy	Condition	Patients (n total)/ follow-up (t)	Evaluated parameters	Results
Chakraborthy 2015/ Randomized clinical trial Level II	Miller's class I and II gingival recessions	(1) Amnion (2) CM	N = 12 t = 6 months	-Gingival index (IG) -Length of recession (GR) -Relative attachment level (RAL) -Width of recession (GRW) -Width of keratinized gingival (WGK) -Root coverage	-Significant improvement of all parameters in both groups compared to baseline -WGK: significantly higher in the CM group at 3 months and no significant difference at 6 months -GRW: significantly higher for the CM group at 3 et 6 months -IG, GR et RAL and root coverage: no significant difference between the groups
Gupta 2018/ randomized clinical trial Level II	Miller's class I and II gingival recessions	(1) Amnion (2) CM	N = 10 t = 6 months	-Plaque index (IP) and gingival index (IG) -Probing pocket depth (PPD) -RAL -Position of gingival margin -Gingival thickness	-IP, IG, RAL and position of gingival margin showed a significant reduction in each group compared to baseline -PDD: no significant difference in both groups -Both groups showed a statistically significant mean increase in the gingival thickness -IP, IG, PPD, RAL and position of gingival margin: no significant difference between the groups -Gingiva was thicker in the chorion group without significant difference
Chopra 2019/ randomized clinical trial Level II	Miller's class I and II gingival recessions	(1) CAF (control) (2) CAF + DFDBA + CM (3) CAF + DFDBA + amnion	N = 30 t = /3 months	-IG -GR -GRW -RAL -Complete/partial root coverage -WGK	-Score IG, GR, GRW and RAL showed a significant reduction in the three groups compared to baseline -A highly significant reduction of GRW was seen in the CM + DFDBA group -A highly significant reduction of GR and a more efficient root coverage was seen in the CM + DFDBA group -WGK significantly increased in all the study groups -CM versus control: CM has significantly better results at 3 months for IG, GRW and WGK; but no significant difference between the groups for RAL et GR -CM versus amnion: GRW and root coverage significantly increased in the CM group versus the amnion group; but no significant difference for the rest of the parameters
Dandekar 2019/ randomized clinical trial Level II	Miller's class I and II gingival recessions	(1) CM (2) PRF	N = 20/ t = 6 months	-Clinical attachment level (CAL) -GR -GRW -WGK -Gingival thickness	-HR, GRW, CAL and WGK: significantly improved in both groups compared to baseline -CM for CAL, GR, WGK and gingival thickness: significantly improved with CM compared to PRF -GRW: no difference between the groups
Pundir 2015/ randomized clinical trial Level II	Miller's class I canine recessions	(1) Amnion (2) CM	N = 6/ t = 6 months	-WGK -PPD -GR -CAL -Gingival biotype	-All parameters were significantly improved in both groups compared to baseline -No significant difference between the groups after 3 and 6 months -9/12 recessions showed 100% root coverage -10/12 recessions developed a thick biotype

TABLE 2 (Continued)

Author/study design (NHMRC)	Using strategy	Condition	Patients (n total)/ follow-up (t)	Evaluated parameters	Results
Nevins 2016/ case series Level IV	Recessions >4 mm	(1) CM	N = 19/ t = 6 months	-IP, IG -PPD -GR -GRW -CAL -WGK	-PPD: no significant difference from baseline -GR, GRW, CAL, WGK: significantly improved -Mean root coverage at 24 weeks: 56%
Esteves 2015/ Retrospective case series Level IV	Miller's class I gingival recessions	(1) CM	N = 6/ t = 6 months	-PPD -CAL -GR -WGK -Gingival thickness	-All parameters were significantly improved at 3 and 6 months compared to baseline -At 6 months, nine recessions with thin biotypes developed thick ones and 14 recessions showed a 100% root coverage -The overall percentage of root coverage: 89.92 ± 15.59%
Temraz 2019/ randomized clinical trial Level II	Intrabony defects >6 mm	(1) ACM (2) DBM (C-blast puttyTM, demineralized bone matrix with cancellous bone)	N = 22/ t = 6 months	Clinical parameters: -IP -IG -PPD -CAL Radiographic parameters: -Bone defect area	-IP: no difference between the groups -IG: significant improvement in both groups -PPD and CAL: significant improvement in both groups at 3 and 6 months compared to baseline; no difference between 3 and 6 months -Bone defect: significant improvement in both groups -No significant difference between both groups at 6 months for all parameters
Kothiwale 2019/ randomized clinical trial Level II	Molar intrabony defects >6 mm	(1) FDBA + CM (2) DFDBA + CM	N = 9/ t = 12 months	Clinical parameters: -IP -IG -PPD -CAL -Mobility Radiographic parameters: -Bone defect area	-IP, IG, PD, CAL, bone defect and mobility significantly reduced at 12 months in both groups compared to baseline -No significant difference between the groups for clinical parameters -Bone density at 12 months was significantly higher in the FDBA + CM groups
Kothiwale 2015/ randomized clinical trial Level II	Intrabony defects >5 mm anterior zone	(1) Open flap debridement (control) (2) CM	N = 5/ t = 6 weeks	-Gingival thickness	-Significant improvement of gingival thickness in the CM group at 6 weeks compared to baseline and to the control
Kothiwale 2018/ randomized clinical trial Level II	Intrabony defects >6 mm Molar zone	(1) Open flap debridement (control) (2) CM	N = 10/ t = 4 weeks	Clinical parameters: -IP -Sulcus bleeding index -PPD -CAL Biochemical parameters: -IL-11 in gingival crevicular fluid	-All clinical parameters were significantly reduced after 4 weeks in both groups compared to baseline -Significantly better results in the CM group (except IP: No difference between the groups) -Significant improvement of biochemical parameters in both groups at 4 weeks -IL-11 levels was significantly increased in the CM group compared to the control group
Kothiwale 2013/ randomized clinical trial Level II	Intrabony defects >5 mm	(1) Open flap debridement (control) (2) CM	N = 10/ t = 1 year	-IG -IP -PPD -RAL -Bone gain area	-Statistically significant improvement of IP, IG, PD, RAL and bone gain in both groups -The results of the CM group were highly better at 12 months for all parameters compared to the control group, except for RAL where the difference between the groups was not significant

(Continues)

TABLE 2 (Continued)

Author/study design (NHMRC)	Using strategy	Condition	Patients (n total)/ follow-up (t)	Evaluated parameters	Results
Holtzclaw 2013/ retrospective case series Level IV	Intrabony defects	(1) Cortical freeze-dried bone allograft +ACM	N = 64/ t = 12 months	-PPD -CAL	-PPD and CAL were reduced at 12 months
Rosen 2015/ case series Level IV	Glickman's class III/IV furcations	1) PDGF-BB + composite allograft + ACM	N = 5/ t = 6 months to 2.5 years	Furcation outcome: -Furcation invasion -PDD -CAL -Periapical radiographic	-3 Furcations closed -2 Furcations reduced to class I in their facial aspect and closed on the lingual aspect -1 Furcation remained in class III
Taalab 2018/ randomized clinical trial Level II	Glickman's class II furcations associated to Miller's class I gingival recessions	(1) Alloplast bone graft (biphasic calcium Phosphat + HA) + ACM (2) Alloplast bone graft (biphasic calcium Phosphat + HA) + collagen membrane	N = 14/ t = 9 months	Clinical parameters: -Healing index of landry (HIL) -PPD -CAL -WGK Radiographic parameters (CBCT): -Horizontal component of the furcation (CHF) -Vertical component of the furcation (CVF)	-HIL: significant increase of healing in the collagen group whereas no significant difference in the ACM group/significant difference between groups with higher collagen content -PPD significantly reduced from baseline to 90 and 180 days for the ACM group/ greater reduction of PPD in the ACM group without significant difference -Significant reduction for CAL from baseline to 90 and 180 days in the ACM group/no difference between groups from baseline to 30 and 90 days, but from baseline to 180 days CAL was significantly reduced in the ACM group compared to the control group -WGK improved in the ACM group without significant difference. No change in the collagen group/the difference between the two was significant at 90 and 180 days where the ACM group was higher. -Significant decrease of CHF in both groups and of CVF in the ACM group compared to baseline -Significantly greater decrease of CHF and CVF in the ACM group compared to the control group
Hassan 2017/ single blind randomized clinical trial Level II	Alveolar ridge preservation in nonmolar zone	(1) ACM + freeze-dried bone (2) dPTFE non absorbable + freeze-dried bone	N = 20/ t = 22 months	Clinical and radiographic parameters (CBCT): -Horizontal and vertical ridge dimensions -Histomorphometric analysis -Microtomographic analysis -Pain score (VAS)	-Clinical and radiographic ridge dimensions were not significantly different between the treatments -Histomorphometric parameters (bone quality) were significantly better with ACM: ACM sites had significantly more osteoids and higher bone density volume, but significantly less graft particles compared to the dPTFE group -VAS was significantly lower for the ACM group the first 2 days
Joshi 2017/ prospective randomized clinical trial Level II	Alveolar ridge preservation in nonmolar zone	(1) FDBA allograft + CM (2) Entire tooth allograft + CM (3) Dentin allograft + CM (4) CM (control)	N = 15/ t = 4 months	Radiographic analysis (CBCT): -Horizontal and vertical ridge dimensions Histologic analysis	-Clinically uneventful healing was observed at all sites -Smaller reduction in alveolar crest height and width in entire tooth and dentin allograft sites compared to the control and the FDBA group -Better integration of graft particles, better osteogenesis and angiogenesis in entire tooth and dentin sites

TABLE 2 (Continued)

Author/study design (NHMRC)	Using strategy	Condition	Patients (n total)/ follow-up (t)	Evaluated parameters	Results
Cullum 2019/ case series Level IV	Alveolar ridge preservation in anterior zone (case 1) and molar zone (case 2)	(1) BioOss/ InnerOss + ACM	N = 2/ case 1: t = 11 months Case 2: t = 1 year	Clinical assessment: -Gingival inflammation Radiological assessment: -Bone healing	-No inflammation -Satisfying bone volume
De Angelis 2019/ case series Level IV	Expansion of the zone of keratinized tissue around dental implants	(1) ACM	N = 15/ t = 1 month	-IP -IS -WGK	-Reduction of IP and IS -Significant increase of WGK from baseline to 7, 15, and 60 days post surgery (average gain = 2 mm)
Holtzclaw 2015/ retrospective case series Level IV	Schneider membrane perforations repair	(1) ACM + freeze-dried cortical bone allograft + ACM	N = 77/ t = 5 years	Implant survival according to Albrektsson criteria	Of the nine cases of perforations, 23 implants placed and one failure Of the 95 cases of nonperforation, 158 implants were placed and three failed
Kakabadze 2016/ case series Level IV	Reconstruction of mandibular defects after tumoral resection	(1) Autogenous bone graft +ACM (2) Biologically active bone + ACM	N = 4/ t = 5 years	Clinical criteria: -Complications occurrence Radiological criteria: -Bone volume	-No complications -Bone volume was maintained

Abbreviations: BDA, bone defect area; CAF, coronally advanced flap; CAL, clinical attachment level; CEJ, cemento-enamel junction; DFDBA, demineralized freeze-dried bone allograft; dPTFE, dense polytetrafluoroetylene; FDBA, fried-dried bone allograft; GR, length of recession; GRW, width of recession; HA, hydroxyapatite; HIL, healing index of landry; IG, gingival index; IP, plaque index; PPD, probing pocket depth; PRF, platelet-rich fibrin; RAL, relative attachment level; WGK, width of keratinized gingival.

series where ACM was used with a composite allograft containing mesenchymal stem cells in a matrix of freeze-dried demineralized bone and freeze-dried bone. An improvement of the furcation defects was observed clinically but the study did not include any statistical analysis.[64]

3.3.2 | Implant and preimplant surgery

Use of CM and ACM for alveolar ridge preservation

Hassan et al. compared ACM to dense polytetrafluoroethylene (dPTFE) membranes. Both membranes were used after extraction sockets filling with freeze-dried bone. No significant difference was observed between the groups for the clinical and radiographic dimensions of the residual ridge. Interestingly, histomorphometric results showed more osteoid tissue, a higher bone density, and less graft particles after 3 months in ACM group. Besides, pain was significantly lower for the ACM group after 24 and 48 hr.[65] Another randomized controlled trial evaluated allogenous tooth graft in comparison with freeze-dried bone allograft. Both grafts were covered by CM. An improvement in clinical parameters was noted in all groups.[66] Finally, a case series reported the absence of inflammation and optimal wound healing after alveolar ridge preservation using a bone substitute (Biooss) covered by ACM.[67]

Use of ACM to increase keratinized tissue around implants

Only one study investigated the effectiveness of ACM to increase keratinized gingiva around dental implants. This was a case series where ACM graft could be performed either at the time of the implant placement or during surgical reopening time (in a two-stage procedure). Application of ACM leads to a gain of 2 mm in keratinized gum width.[68]

Use of CM and ACM to repair Schneider membrane in sinus elevation procedure

A case series reported the efficacity of ACM in repairing perforations of the maxillary sinus membrane perforations. However, only one study with a weak level of evidence has been conducted.[69]

3.3.3 | Use of CM and ACM to repair large mandibular defects

Kakabadze et al. used ACM for covering mandibular reconstructions after segmental mandibulectomy following tumor resection. Only one series of four cases was identified, and it was focused on the bone graft evaluation (autogenous versus bioactive bone). All bone transplants were covered with ACM and no failure was noted. ACM membranes fulfilled their role of protection against fibrous tissue invasion between the bone graft and the host bone.[70]

4 | DISCUSSION

The objective of this systematic review was to report the current clinical applications of CM and ACM, as well as their treatment modalities, in oral and periodontal surgery.

Among the 21 included articles, CM and ACM were processed using four different preservation methods. Membranes were dehydrated in 11 studies and this dehydration was mostly preceded by de-epithelialization (Purion process). They were freeze-dried in eight studies. Lyophilization was preceded by decellularization in one study. The freeze-dried and dehydrated membranes were subsequently sterilized by γ radiation. Such sterilization procedures allow membrane storage at room temperature for several years. Although the included studies did not investigate this parameter, preservation methods might affect the extracellular matrix of the basement membrane and lead to change in the membrane's biological and mechanical properties.[35] Freeze-drying appears to decrease the thickness and strength of the membrane, but it improves the adhesion properties compared to fresh and cryopreserved membranes.[71] The Purion process is a de-epithelialization followed by gentle dehydration that preserves structural integrity and biochemical activity of the tissues.[68] After decellularization and lyophilization, the majority of growth factors and cytokines and their structural and mechanical properties seem to be preserved.[72-74] The biological properties of dehydrated ACM grafts have been investigated in other studies: cytokines, chemokines, growth factors, and therefore biological activities were still present after preservation.[74,75] In our review, these parameters were not investigated and the heterogeneity of preservation methods makes the results difficult to compare.

In this study, we mainly identified seven clinical applications of CM and ACM in oral and periodontal surgery: gingival recession treatment, intrabony and furcation defect treatment, alveolar ridge preservation, keratinized gum width increase around dental implants, Schneiderian membrane repair and large bone defect reconstruction. CM and ACM were compared to a conventional surgery without membrane or to the following materials: collagen membranes, dPTFE membranes, PRF membranes, amnion membranes, and to a bone substitute.

CM and ACM were superior to PRF membranes and amnion in gingival recessions treatment.[53,55,56] ACM showed better clinical and radiological results than a collagen membrane for furcations treatment.[63] One study reported no significant difference between ACM and a bone substitute used alone in the treatment of intrabony defects.[59] Three studies reported a significant improvement in treating periodontal pockets using CM compared to conventional surgery (open flap debridement).[3,60,62] Promising results were also observed using CM and ACM for alveolar ridge preservation.[65-67] ACM showed similar results than a conventional nonresorbable membrane for post-extraction ridge preservation, as no significant difference in ridge volume dimensions were recorded. Besides histological analysis showed a better bone quality using ACM.[65] These studies also reported the absence of post-operative inflammation and satisfactory bone healing was radiologically observed using CM and ACM.[66,67] For all these clinical indications, using CM or ACM showed better or comparable results to conventional biomaterials. This could be explained, among other things, by their attractive biological properties. The use of CM and ACM for keratinized gum width increase around dental implants, Schneiderian membrane repair as well as to cover large bone defects reconstruction were only investigated through case series.[68-70] While satisfactory results were obtained, studies with higher levels of evidence are needed to draw some conclusions for these applications.

In all included studies, CM and ACM were used in allografts and no rejection reactions were reported. in vitro studies have shown that amniotic and chorionic cells do not trigger an immune response and suppress lymphocyte proliferation. Fetal membranes have low immunogenicity, which reduces the risk of complications in comparison with xenografts.[76] They do not express classical HLA class I antigens or HLA class II antigens, which protects them from a defensive response. They also express nonclassical immunoregulatory antigens such as HLA-G.[77]

No inflammatory or infectious complications were observed postoperatively in the selected articles. The risk of infection is decreased thanks to the antiviral and antimicrobial properties of these fetal membranes. Talmi et al. emphasized the antibacterial properties of fetal membranes in 1991.[78] Since then, the antimicrobial and antibiofilm properties of AM and CM against *Streptococcus pneumoniae*, found in the nasopharynx, were highlighted by Yadav et al. in 2017.[79] More specific studies on the endobuccal flora lead to the same conclusions. Ashraf et al. highlighted the bactericidal activity of ACM in vitro, whereas the control collagen membrane has not demonstrated any anti-bacterial activity.[11] The powerful adhesive properties of the membranes prevent the formation of a gap between the barrier membrane and the defect, especially in irregular areas, which would also reduce the risk of infection. CM and ACM were left exposed voluntarily in four studies.[65-68] Unlike conventional membranes CM and ACM demonstrate antibacterial properties. It is thus possible to leave them exposed without risk of infection, thereby avoiding the inconvenience of flap traction. Some authors reported that dPTFE membranes could also be left exposed, especially since their pores are smaller than conventional PTFE membranes, which were permeable to bacteria. However, dPTFE membranes remain nonresorbable and biologically inert.[65] Moreover, placental membranes possess anti-inflammatory properties. These membranes reduce inflammation by capturing inflammation cells,[12] and express interleukin receptor antagonists, endostatins, TIMP 1,2,3,4 matrix metalloproteinase inhibitors, and anti-inflammatory proteins.[4]

Promising results were achieved using CM/ACM to regenerate oral soft tissue. The amnion/chorion tissue secretes an abundance of growth factors (KGF, b-FGF, TGF-beta, EGF…) that can promote epithelialization and soft tissue regeneration. Derived membranes therefore tend to promote rapid epithelialization rather than functioning by epithelial exclusion like traditional membranes. Instead, the epithelial cells can proliferate and form a seal along the membrane, and this newly formed junctional epithelium allows an early isolation of the defect.[63,80] Hassan et al. evaluated that complete wound

epithelialization occurred in approximately 2 weeks at ACM sites due to the presence of growth factors. In dPTFE sites soft tissue closure occurs below the membrane and epithelialization occurs only after removal of the membrane.[65] Amnion/chorion possess antifibrotic properties by inhibiting TGF β.[12] It also has an angiogenic potential and secretes growth factors such as angiogenin or VEGF.[81] An increased neovascularization using dehydrated ACM was observed in a mouse model of subcutaneous implantation.[5]

Some growth factors contained in CM/ACM may also induce bone regeneration.[49,81-83] In their study, Taalab et al. explain the improvement of furcation components by this osteogenic differentiation promoted by the ability of ACM to recruit progenitor cells.[63] Kakabadze et al. also found that the use of ACM for the reconstruction of mandibular bone defects improved osseointegration and provided strong protection against fibrous tissue invasion between the bone graft and the native host bone.[70] Hassan et al. reported an "improved bone quality" characterized by better histological and morphological parameters, which was attributed to the preservation of the bioactivity of ACM. A higher amount of osteoids and a smaller number of graft particles suggesting a faster bone turnover with ACM compared to PTFE sites, thereby implying that implants can be placed sooner in sites preserved with ACM and into better bone quality.[65] A single blind randomized controlled clinical trial compared PTFE membranes and commercially available BioXclude ACM in the preservation of alveoli filled with a freeze-dried bone allograft. The author found no significant difference in peak volume maintenance or pain score between the groups.[84]

Several studies also highlighted the analgesic properties of CM and ACM. When reported, the authors described mild pain and discomfort. Hassan et al. evaluated a lower pain scale (Visual Analog Score) using CM compared to dPTFE membranes.[65] De Angelis et al. reported a low post-operative pain score for sites treated with ACM,[68] whereas Chopra et al. found no significant difference between the chorion, amnion, and control groups.[55] In a recent randomized controlled trial, Cazzell et al. concluded that there was a significant reduction in pain in patients treated with dehydrated ACM.[85] Another study also reported the beneficial effect of dehydrated ACM injection in reducing pain in the treatment of tendonitis and arthritis.[86] The abovementioned inherent biological properties of placental membranes (growth factors modulating inflammation and regeneration) and physical properties (close adaptation on irregular defects and coverage of exposed nerve endings) enhance wound healing and may contribute to reduce pain.[85,87]

CM and ACM measure around 300 μm thick and therefore easier to handle than an amnion-only membrane (less than 100 μm thick), but more flexible than collagen membranes (300–800 μm).[88] In our review, all the studies used single-layer membranes whereas the amnion alone is often used as a multilayer membrane.[47] An easy adaptation to the defect is often reported, and the self-adhering properties of CM and ACM increase their stability. Other advantages have been highlighted such as their capacity to self-hydrate with blood, or the possibility to leave it as such if it folds on itself together. These membranes did thus not require and a precise cut. Most authors also agreed that there is no need to suture CM and ACM thanks to an intimate adaptation to the defect.[3,37,52-54,56-59,61-64,69] Another advantage of placental membranes is their spontaneous resorption, thus avoiding a second surgical step. Their resorption does not interfere with tissue healing process because it does not lead to the formation of foreign bodies or empty spaces.[89] Only few studies investigated their resorption times. Taalab et al. reported using a BioXclude ACM with 8–12 weeks of resorption,[63] whereas Chopra et al. used a dehydrated CM that would be resorbed in two to 4 weeks.[55] Other studies must be conducted to further specify resorption time and compare it with conventional resorbable membranes.

5 | CONCLUSION

Several studies now support the use of CM and ACM to regenerate oral soft and hard tissues. Despite this, more studies investigating the benefit of using these biological membranes, compared to conventionally used membranes, have to be conducted.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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