Effectiveness of Amniotic Membrane with Coronally Advanced Flap in the Treatment of Gingival Recession in Adult Patients: A Systematic Review

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ABSTRACT

Aim and objective: To evaluate the effectiveness of amnion membrane on the clinical parameters when used in the treatment of Millers Class I and Class II gingival recession in chronic periodontitis patients along with coronally advanced flap (CAF).

Data resources: Four databases MEDLINE (by PubMed), Cochrane database, EBSCO, and Google Scholar were explored to identify the studies in English up to April 2020. An additional hand search of relevant journals was also done. Two independent reviewers screened the retrieved articles using the particular inclusion criteria. Randomized control trials (RCTs) evaluating the effectiveness of amnion membrane with CAF in treatment of Millers Class I and Class II gingival recession in chronic periodontitis patients were included in the study. Outcome variables examined were recession width (RW), recession depth (RD), clinical attachment level (CAL), keratinized width of gingiva (KWG), probing pocket depth (PPD), and gingival thickness (GT). Data were analyzed using Revman5.3 software. The mean differences and 95% confidence interval were used to illustrate the estimate of effect size.

Study selection: Seven relevant articles were recognized for data procurement. One hundred and twenty patients with 244 gingival recession sites in total with an age range between 18 years and 55 years of participants were selected. There is an equal effect in both the groups for the RD reduction. For RW reduction, the result was in the favor of amnion membrane with CAF group, whereas for CAL gain, PD reduction, KWG gain, and GT gain results favored the different biomaterial other than amnion membrane but no statistical significant difference was found.

Conclusion: Within the limitation of the study, it seems that the amnion membrane can be used successfully along with CAF to treat the gingival recession.

Keywords: Amnion membrane, Chronic periodontitis, Coronally advanced flap, Gingival recession, Placental membrane, Root coverage, Systematic review.

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INTRODUCTION

“Gingival recession (GR) is the change in the position of the marginal part of the gums apically to the cementoenamel junction (CEJ) with denudation of the root surface”. It is induced due to pathological, anatomical, and traumatic factors.1 It is responsible for esthetic concern, difficulty in oral hygiene maintenance, loss of the tooth, root sensitivity, and root caries.2 Gingival recession is seen in subjects with periodontal disease as well as with good oral hygiene.3 The gingival recession of 1 mm or more in one or more sites is seen in 50% of the population.4

For the root coverage of single or multiple recessions, several newer and advanced techniques of periodontal plastic surgery have been propounded. Coronally advanced flap (CAF) is a commonly used mucogingival procedure where the gingival flap is shifted coronally over the exposed root surface. Evidence suggests that CAF is a predictable as well as an effective technique since the results of root coverage are favorable with good color blending, restores the original morphology of the treated gingival site postoperatively.5 The procedure is convenient and less invasive since no graft is harvested when treated with CAF alone. However, it was reported that the result of root coverage is not stable in a long-term follow-up. The root coverage was 89% at 1 month and declined to 58.8% at a 6-month postoperative follow-up.6 In CAF, healing occurs by repair (forming long junctional epithelium) and not by regeneration. Thus, it is often combined with many biological factors or regenerative materials following the technique based on the GTR principle.

The gold standard technique for the treatment of gingival recession is coronally advanced flap (CAF) along with connective tissue graft (CTG).7 But the need for donor tissue that results in a second surgical site is the main disadvantage of the CTG technique. It also causes patient discomfort, postoperative pain, and a large amount of tissue is needed to treat multiple recessions.8 Thus, alternative grafts and biomaterials recommended are autologous plasma,9 enamel matrix derivatives (EMDs),9 acellular dermal matrices,10 chorion membrane,11 amnion membrane,12 and collagen membrane.13

Amnion membrane was first used by Davis in 1910.14 It is a tough, thin, transparent, avascular composite allograft membrane
of different layers such as thin epithelium, a thick basement membrane, and an avascular mesenchyme pieced of collagen mainly.\textsuperscript{15} Owing to the presence of various growth factors like epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), transforming growth factor-α (TGF-α), transforming growth factor-β (TGF-β), and keratinocyte growth factor (KGF), it induces angiogenesis, reduces the pain, and promotes epithelialization and extracellular matrix deposition. It has a variety of specialized proteins like proteoglycan, fibronectin, laminin, and collagen type I, IV, V, and VII. It also possess various biological properties such as anti-inflammatory, antiviral, antimicrobial, anti-scarring, and immunomodulatory.\textsuperscript{16} Thus, a third generation bioresorable amniotic membrane provides the structural as well as anatomical arrangement of regenerated tissues, boost the gingival wound healing and augments a rich source of stem cell thus advocated in various periodontal plastic surgical procedures.\textsuperscript{17}

Thus, this systematic review aimed to evaluate the effectiveness of amnion membrane in comparison with different biomaterials when used with CAF for root coverage in chronic periodontitis patients.

**Materials and Methods**

**Protocol and Registration**

To avoid any unintentional reiteration of the review on this topic, registration of the review protocol was done at an international database of prospectively registered systematic reviews PROSPERO (CRD42020175541). We composed the review as per Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines\textsuperscript{18,19} and also ensued PRISMA statement and Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{20,21} Our review question was: “What is the effectiveness of amnion membrane with Coronally Advanced Flap in the treatment of gingival recession in adult patients”\textsuperscript{22}

**Focused PICOS Question**

The following PICOS model was employed for this review:

**P**—Chronic periodontitis patients with Miller’s Class I or Class II localized gingival recession.

**I**—Interventions being evaluated was the surgical technique of CAF in combination with amnion membrane.

**C**—Comparison was done with the surgical technique of CAF in combination with different biomaterials other than amnion membrane.

**O**—Different type of outcome being measured were

- Primary outcome:
  - Gingival recession depth (RD)
  - Gingival recession width (RW)
  - Width of keratinized gingiva (KWD)

- Secondary outcomes:
  - Probing pocket depth (PD)
  - Gingival biotype (GT)
  - Clinical attachment level (CAL)

In the included studies, all these clinical parameters were evaluated for a period of a minimum 6-month postoperatively.

**S**—Studies searched were randomized controlled clinical trials (RCTs), published only in the English language and restricted to human gingival recession defect.

**Search Strategy**

We executed a comprehensive literature search up to April 2020. All randomized control clinical trials done on the human gingival tissues were scouted in four databases MEDLINE (by PubMed), EBSCO, Cochrane Database, and Google Scholar. Journals like Journal of Periodontal Research, Journal of Clinical Periodontology, Journal of Periodontal Research, and International Journal of Periodontics and Restorative Dentistry were hand searched to recover additional articles. Even the references list of relevant articles were appraised.

The electronic search included the following terms: (“amnion membrane” OR “placental membrane” OR “amnion”) AND (“coronally advanced flap”) AND (“Class I” OR “Class II”) AND (“gingival recessions” OR “root coverage”) AND (“randomized controlled trial”).

**Inclusion and Exclusion Criteria**

**Inclusion Criteria**

- Subjects who are systemically healthy having age >18 years
- Patients diagnosed with chronic periodontitis having a defect of Miller’s Class I or Class II gingival recessions.
- Patients who can maintain good oral hygiene.
- Both males and females subjects were included.
- Patients who are willing to take part in the study and report for regular follow-up.

**Exclusion Criteria**

- Subjects having a habit of smoking.
- Female patients who are lactating or pregnant during the study period.
- Patients treated for periodontal disease in the last 6 months
- Subjects who fail to maintain good oral hygiene.

**Screening and Data Extraction**

Two reviewers independently screened the title and abstract of the initially identified studies. Any duplication or articles that do not meet inclusion criteria were exempted. Full-text copy for all eligible articles was obtained and two reviewers assessed them separately to determine whether they qualify the inclusion norms. Any disagreement was resolved by discussion. Articles were excluded if they were not as per the inclusion norms. The reasons for exclusion were recited. In a Microsoft excel sheet, the data of the included studies were extracted.

For the meta-analysis, the clinical parameters (i.e., RD, RW, KTW, PD, CAL, and GT) were collected from the included studies. If the included studies did not disclose the mean difference and standard deviation of the clinical parameters assessed (difference between follow-up and baseline), a further calculation of the mean difference would be requested. For each comparison, the initial step was to calculate the intragroup mean difference between baseline and follow-up.

\[
\text{Intragroup mean difference} = (\text{Follow-up data of control group}) - (\text{Baseline data of control group})
\]

\[
\delta \text{ Mean}_{\text{ctrl}} = (\text{Follow-up data of test group}) - (\text{Baseline data of test group})
\]

The second step was to calculate the intergroup difference by:

\[
\Delta \text{ Mean} = \delta \text{ Mean}_{\text{ctrl}} - \delta \text{ Mean}_{\text{test}}
\]
Outcome Measurements

Primary Outcome

- Change in RD was reported as a reduction in recession at the 6-month follow-up evaluation (RD was measured at the mid-buccal from CEJ to the gingival margin).
- Change in RW was reported as a reduction in RW at the 6-month follow-up evaluation (RW was measured at the buccal surface at the level of the CEJ from the mesial most to the distal-most of the gingiva).
- Change in KTW was reported as gain in KTW at the 6-month follow-up evaluation (KTW was measured as the distance from the mucogingival junction to the free gingival margin).

Secondary Outcome

- Change in PD was reported as a reduction in PD at the 6-month follow-up evaluation (PD was measured from margin of free gingiva to periodontal pocket).
- Change in CAL was reported as a reduction in CAL at the 6-month follow-up evaluation (CAL was referred to as the distance from the CEJ to the most apical part of the sulcus).
- Change in GT was reported as gain in GT at the 6-month follow-up evaluation (GT was measured 3 mm below the gingival margin at the level of attached gingiva).

Risk of Bias

Two investigators appraised the quality of selected studies separately using the risk of bias assessment tool (The Cochrane collaboration’s tool). If any debate over a review, then it was settled by conversation. By using the risk of bias assessment tool, the studies were categorized as a high, low, or unclear risk of bias. After the quality assessment, the studies were categorized as: (1) low risk: when all criteria were met or one criterion was unclear/not met; (2) moderate risk: when two criteria were unclear/not met; (3) high risk: when more than two criteria were not met. As per the Cochrane handbook, Chi-square and Higgins index ($I^2$) were used to decide the heterogeneity.

Statistical Analysis

For the meta-analysis, Revman5.3 (Review Manager Version 5.3; The Cochrane Collaboration, Copenhagen, Denmark) software was employed for the included studies. The continuous data (including RD, RW, KTW, PD, CAL, and GT) were estimated as mean difference (MD) and 95% confidence interval (CI), with $p < 0.05$ being statistically significant. The fixed-effect model was applied when the heterogeneity between the studies was low ($p ≥ 0.10$, $I^2 ≤ 50\%$) and when heterogeneity was high ($p < 0.10$, $I^2 > 50\%$), the random effect models were applied for meta-analysis. The heterogeneity across studies in RD, RW, WKG, CAL, PD, and GT were correlated through subgroup analysis. The results of meta-analysis were represented in the forest plot.

Results

Study Selection

Two hundred and ninety studies were identified after the initial electronic search and only two studies were obtained by hand search. After duplicate removal, 121 records were screened for title and abstract, 111 articles were eliminated, and remaining 10 articles were scrutinized for full text. Three articles were excluded after the full text evaluation because one study reported insufficient follow-up period and even bone graft (DFDBA) was used along with amnion membrane and in other two studies no biomaterials were utilized along with CAF for control group. Finally seven studies were selected for data extraction. The selection process was outlined in the PRISMA flowchart (Flowchart 1).

Study Characteristic

Total 120 patients with 244 sites with either Millers Class I or Class II gingival recession were included except in Rehan et al.'s study where only Millers Class I gingival recession sites were enrolled. A maximum of 30 patients participated in Jain et al.'s study, whereas a minimum of 10 patients participated in Rehan et al.'s study. Ghae and et al.'s study included a maximum of 71 sites, whereas Rehan et al.'s study included a minimum of 10 sites. Three articles were according to a split-mouth study design and four articles followed a parallel study design. The age
range of the participants was between 18 years and 55 years in all the studies except in the study of Agarwal et al., age was not mentioned. The mean age of participants was intimated in the study of Chakraborthy et al. and Lafzi et al. Five studies described gender distribution of patients and in one study only male patients were included. In all the included studies minimum follow-up was of 6 months. Maximum of 18-month follow-up was mentioned in Rehan et al.’s study. Since it is a surgical procedure, it was not possible to be blind to the patients. In Rehan et al.’s study, only patients were blinded whereas in Lafzi et al.’s study only assessors were blind. In one article, the patients and the assessors were both were blind while in the remaining four articles it was unclear. All the studies had complete follow-up reports. None of the study stated selective reporting and other biases. On evaluation, one article was claimed as low risk, two articles as moderate risk (when two criteria were not met or unclear), and four articles as high risk (when three or four criteria were not met or unclear). Figure 1 summarizes the quality assessment of the included studies.

**Quality of Studies**

All the seven articles mentioned sequence generation: two articles used a flip a coin method, and one used chit method, one lottery method, and the remaining three articles did not explain the method of random sequence generation. Out of seven included articles, six articles did not account allocation concealment, whereas one article intimated it. Since it is a surgical procedure, it was not possible to be blind to the patients. In Rehan et al.’s study, only patients were blinded whereas in Lafzi et al.’s study only assessors were blind. In one article, the patients and the assessors were both were blind while in the remaining four articles it was unclear. All the studies had complete follow-up reports. None of the study stated selective reporting and other biases. On evaluation, one article was claimed as low risk, two articles as moderate risk (when two criteria were not met or unclear), and four articles as high risk (when three or four criteria were not met or unclear). Figure 1 summarizes the quality assessment of the included studies.

**Outcome**

**RD Reduction**

Seven studies were included in the meta-analysis. A model employed was a fixed-effects model. According to the result obtained the use of amnion membrane and other biomaterials along with CAF caused an equal reduction in RD in the treatment of gingival recessions (Fig. 2A). No significant difference was found for CTG, PRF, collagen, and chorion group as per subgroup analysis.

**RW Reduction**

The meta-analysis for RW reduction was performed on five studies. Two studies were excluded for their incomplete data. A model employed was a random-effects model. The results manifested that the use of amnion membrane along with CAF causes a reduction in RW in the treatment of gingival recessions (Fig. 2B). No significant difference was found for CTG, PRF, and chorion group according to the subgroup analysis.

**Keratinized Width of Gingiva Gain**

The meta-analysis was performed on five studies for keratinized width of gingiva (KWG) gain. Two articles did not provide specific data thus were excluded from the meta-analysis. A model employed was a fixed-effects model. The results manifested that the use of different biomaterial groups (other than amnion membrane) caused a reduction in KGW when combined with CAF in the treatment of gingival recessions (Fig. 2C). As per the results of the subgroup analysis, only chorion membrane could significantly improve the KTW, with an MD of 0.09 mm (95% CI: 0.07–0.26 mm; p = 0.04). A significant difference was not found in the subgroup of CTG and PRF groups.

**PD Reduction**

The meta-analysis for PD reduction was performed on four studies. Three studies were excluded for its incomplete data. A model employed was fixed-effects model. The results revealed that in the treatment of gingival recessions the use of different biomaterial group (other than amnion membrane) caused a reduction in PD when added to CAF (Fig. 2D). No significant difference was found for CTG, PRF, and collagen group as per subgroup analysis.

**Table 1: General information of included studies**

| Author          | Publication year/place | Journal                                  | Age range       | Gender          | Follow-up    | Intervention               |
|-----------------|------------------------|------------------------------------------|-----------------|-----------------|--------------|---------------------------|
| Ghahroudi et al. | 2014/Iran              | International Academy of Periodontology  | Above 18 years  | Male-30, Female-41 | 3, 6 months  | CAF+ amnion membrane      |
| Chakraborthy et al. | 2015/India            | Journal of Clinical and Diagnostic Research | 33.5 ± 6.89 years | Not specified   | 1, 3, 6 months | CAF+ amnion membrane      |
| Lafzi et al.    | 2016/Iran              | Journal of Dental Restorative, Dental Prospects | 34 ± 12 years  | Not specified   | 1,3,6 months | CAF+ amnion membrane      |
| Agarwal et al.  | 2016/India             | European Journal of Dentistry            | Not specified   | Males-18, Females-5 | 3, 6 months  | CAF+ amnion membrane      |
| Jain et al.     | 2017/India             | Journal of Clinical and Diagnostic Research | 18–55           | Males-15, Females-15 | 3, 6 months  | CAF+ dehydrated amnion membrane |
| Mahajan et al.  | 2018/India             | Journal of Indian society of periodontology | 18–40           | Males-5, Females-7 | 3, 6 months  | CAF+ amnion membrane      |
| Rehan et al.    | 2018/India             | Contemporary Clinical Dentistry           | 20–45 years     | Males-10         | 6, 18 months | CAF+ amnion membrane      |
CAL Reduction

The meta-analysis was performed in five studies. Two studies\textsuperscript{24,27} were excluded as they provided incomplete data. A fixed-effects model was employed ($I^2 = 0\%$) since there was no reported heterogeneity. The results exhibited that in the treatment of gingival recessions the use of different biomaterial groups (other than amnion membrane) caused a gain of CAL when added to CAF (Fig. 2E). No significant difference was found for CTG, PRF, and collagen group as per subgroup analysis.

GT Gain

Three studies\textsuperscript{24,25,27} out of seven were excluded from meta-analysis as there was incomplete data. As the heterogeneity was high ($I^2 = 98.4\%$) a random-effect model was employed. According to the results of our meta-analysis different biomaterial groups other than amnion membrane exhibited significant difference for collagen membrane group, with an MD of 0.86 mm (95% CI: 0.75–0.97 mm; $p < 0.00001$) but for the CTG and PRF groups, no significant difference was intimated.

**DISCUSSION**

Ever since CAF was introduced by Norberg in 1926 researchers have done enormous work to achieve predictable, less invasive, and effective outcomes from this surgical procedure. But in the case of CAF, many surgical defects regenerate incompletely since the formation of long junctional epithelium occurs by an invasion of the epithelial cell into the defect which plays a vital role in repair and not regeneration.\textsuperscript{32} So, the technique based on the GTR principle is used where CAF is combined with different biomaterials like PRF, amnion, chorion, collagen, and ADM which act as a barrier membrane so as to improve the result.\textsuperscript{33}

Amnion membrane has shown exceptional biocompatibility, good healing capacity with easy availability at an affordable cost having a good shelf life. Moreover, to a great extent, it resembles the basement membrane of human oral mucosa,\textsuperscript{34,35} so this membrane have been suited for the treatment of different periodontal conditions like furcation defects,\textsuperscript{36} intrabony defects,\textsuperscript{37} and gingival recession. The clinical evidence was insufficient to conform reconfil the effect of amnion membrane, so this review was intended to compare the effectiveness of amnion membrane with CAF in the treatment of gingival recession in adult patients.

Only RCTs were scrutinized for this systematic review; to avoid serious methodological flaws and to get stronger evidence for the systematic review. Miller’s Class I and II gingival recession shows the highest success rates for root coverage procedures.\textsuperscript{38} So, the studies with the patients diagnosed with chronic periodontitis and having Miller’s Class I and II recession were only included. Smokers were eliminated in all studies as they negatively influence CAL gain and gingival recession reduction.\textsuperscript{39}

Regarding the outcome, there is an equal effect by both the groups for the RD reduction. But in the case of RW reduction, the results were in favor of amnion membrane with CAF group but the difference was not statistically significant. Heterogeneity of RW seems to be linked to the different surgical techniques like in Agarwal et al.’s\textsuperscript{26} study microsurgical protocol was used, in Lafzi et al.’s\textsuperscript{25} study, only partial-thickness flap was elevated, in Chakraborthy et al.’s\textsuperscript{24} study root biomodification with EDTA was performed whereas in Ghahroudi et al.’s\textsuperscript{23} study tetracycline was applied for 2 minutes over the exposed root surface. In terms of PD reduction, CAL gain, KWT, and GT gain different biomaterial (CTG, PRF, and collagen) exhibited effective results along with CAF but the difference was not statistically significant. Heterogeneity in GT seems to be because of different technique employed for

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**Table 2: Data of included studies**

| Reference (year) | MD in RD between baseline and 6 months follow-up (mm) | MD in RW between baseline and 6 months follow-up (mm) | MD in WKG between baseline and 6 months follow-up (mm) | MD in PD between baseline and 6 months follow-up (mm) | MD in CAL between baseline and 6 months follow-up (mm) | MD in gingival biotype between baseline and 6 months follow-up (mm) | Other outcome |
|------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------|--------------|
| Ghahroudi et al. (2014) | 2.4 ± 1.654 | 1.5 ± 1.739 | NR | NR | 2.4 ± 1.40 | 0.8 ± 1.57 | Papilla dimension |
| Chakraborthy et al. (2015) | 2.3 ± 1.594 | 2.7 ± 1.561 | NR | NR | 2.2 ± 1.892 | 1 ± 1.39 | PI, GI, RAL, % root coverage |
| Lafzi et al. (2016) | 2.00 ± 0.85 | 2.50 ± 1.17 | 1.00 ± 0.51 | NR | NR | NR | % root coverage |
| Agarwal et al. (2016) | 2.1 ± 1.13 | 2.7 ± 1.45 | 0.11 ± 0.3 | 0.15 ± 0.36 | 2.14 ± 1.30 | NR | |
| Jain et al. (2017) | 1.5 ± 0.99 | 1.8 ± 1.79 | 1.4 ± 1.56 | 0.3 ± 0.79 | 1.52 ± 1.73 | −0.01 ± 0.15 | PI, GI, AG, PCS, PES, HS |
| Mahajan et al. (2018) | 1.81 ± 0.97 | NR | 0.69 ± 0.60 | NR | NR | NR | |
| Rehan et al. (2018) | 2.33 ± 0.86 | NR | NR | 0.2 ± 0.33 | 2.45 ± 0.89 | −0.63 ± 0.13 | PI, GI |
| | 1.83 ± 0.91 | NR | NR | 0.25 ± 0.54 | 2.20 ± 1.19 | −1.49 ± 0.14 | |
| | 1.80 ± 0.92 | 0.30 ± 0.48 | 1.10 ± 1.10 | 0.20 ± 0.63 | 1.50 ± 1.35 | −0.20 ± 0.42 | |
| | 1.50 ± 1.53 | 0.20 ± 0.42 | 0.80 ± 1.03 | 0.30 ± 1.34 | 1.00 ± 1.05 | −0.20 ± 0.42 | |
measurement of GT in different studies. Gain in CAL suggests periodontal regeneration, new attachment or reattachment but due to the lack of histological evidence in all of the included study the actual phenomenon behind gain in clinical attachment level cannot be explained.28

For KWT gain, statistically significant difference was found in the study where chorion membrane was used along with CAF which was similar to the result found in Sharma et al.’s17 study.

GT gain in the collagen membrane group demonstrated a statistically significant difference which is attributed due to the thickness of the amnion membrane is around 300 nm in cross-section, unlike collagen membrane which averages around 750 nm.40 Degradation of collagen membrane is slow it takes around 6–8 weeks. Space created by the barrier membranes with clot formation leads to cellular proliferation and migration which may be responsible to increase the thickness of the gingival biotype. Later as the barrier membrane is degraded by the host enzymes secondary space is created which further increases the thickness of the gingival tissue.28 The results observed were similar to the findings of Cardaropoli and Cardaropoli.

It is important to consider that the results may be affected significantly by other factors also such as flap tension, soft tissue thickness, and experience of the operator.
CONCLUSION
Thus, within the limitation of the study, it seems that the amnion membrane can be used successfully along with CAF for the treatment of gingival recession.

But only a tentative conclusion can be drawn from this study since there is a limited number of studies with restricted data, a follow-up period of short duration, and having a comparatively high risk of bias. Hence, higher quality RCTs with longer follow-up and substantial sample size are needed to draw a definitive conclusion.
### Table 2: Comparison of Mean Differences Between Experimental and Control Groups

| Study or Subgroup | Experimental Mean | Experimental SD | Control Mean | Control SD | Mean Difference (IV, Fixed, 95% CI) | Mean Difference (IV, Fixed, 95% CI) |
|-------------------|-------------------|-----------------|--------------|------------|------------------------------------|------------------------------------|
| 1.3.1 CTG         |                   |                 |              |            |                                    |                                    |
| lazfiz et al. 2016| 0.11              | 0.3             | 0.11         | 0.4        | 15 55.7% 0.00 [-0.25, 0.25]         |                                    |
| Ghuloudi et al. 2014| 2.4               | 1.654           | 2.31.594     | 15         | 55.7% 0.00 [-0.25, 0.25]           |                                    |
| Subtotal (95% CI) | 57                | 44              | 25.4%        |            |                                    |                                    |
| Heterogeneity: Not applicable |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 0.00 (P = 1.00) |            |                 |              |            |                                    |                                    |

| 1.3.2 PRF         |                   |                 |              |            |                                    |                                    |
| Agrawal et al. 2016| 0.99              | 1.56            | 1.4          | 1.56       | 15 2.9% -0.41 [-1.53, 0.71]         |                                    |
| Ankitra J et al. 2017| 0.89              | 0.6             | 0.55         | 0.72       | 15 15.0% 0.14 [-0.33, 0.61]         |                                    |
| Rehan et al. 2018  | 1.1               | 1.1             | 1.8          | 1.03       | 10 4.1% 0.70 [-1.63, 0.23]          |                                    |
| Subtotal (95% CI) | 40                | 40              | 22.8%        |            |                                    |                                    |
| Heterogeneity: Not applicable |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 2.02 (P = 0.04) |            |                 |              |            |                                    |                                    |

| 1.3.3 CHORION      |                   |                 |              |            |                                    |                                    |
| Sonali chakraborty et al. 2015| 1.42          | 0.51            | 1           | 0.51       | 12 21.4% -0.42 [0.01, 0.83]         |                                    |
| Subtotal (95% CI) | 12                | 12              | 21.4%        |            |                                    |                                    |
| Heterogeneity: Not applicable |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 0.02 (P = 0.04) |            |                 |              |            |                                    |                                    |

Total (95% CI): 67 67 100.0% 0.07 [-0.12, 0.26] Favors [Experimental] Favors [Control]

### Table 3: Comparison of Mean Differences Between Experimental and Control Groups

| Study or Subgroup | Experimental Mean | Experimental SD | Control Mean | Control SD | Mean Difference (IV, Fixed, 95% CI) | Mean Difference (IV, Fixed, 95% CI) |
|-------------------|-------------------|-----------------|--------------|------------|------------------------------------|------------------------------------|
| 1.4.1 CTG         |                   |                 |              |            |                                    |                                    |
| lazfiz et al. 2016| 0.15              | 0.35            | 0.15         | 0.36       | 15 83.3% 0.00 [-0.25, 0.25]         |                                    |
| Subtotal (95% CI) | 15                | 15              | 83.3%        |            |                                    |                                    |
| Heterogeneity: Not applicable |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 0.00 (P = 1.00) |            |                 |              |            |                                    |                                    |

| 1.4.2 PRF         |                   |                 |              |            |                                    |                                    |
| Agrawal et al. 2016| 1.2               | 1.39            | 1.52         | 1.73       | 15 4.3% -0.32 [-1.44, 0.80]         |                                    |
| Rehan et al. 2018  | 1.5               | 1.35            | 1.05         | 1.05       | 10 4.8% 0.50 [-0.56, 1.56]          |                                    |
| Subtotal (95% CI) | 25                | 25              | 9.1%         |            |                                    |                                    |
| Heterogeneity: Chi2 = 1.08, df = 1 (p = 0.30); I2 = 8% |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 0.29 (P = 0.77) |            |                 |              |            |                                    |                                    |

| 1.4.3 CHORION      |                   |                 |              |            |                                    |                                    |
| Mahajan et al. 2018| 2.45              | 0.89            | 2.2          | 1.19       | 12 7.6% -0.25 [0.59, 1.09]          |                                    |
| Subtotal (95% CI) | 12                | 12              | 7.6%         |            |                                    |                                    |
| Heterogeneity: Not applicable |            |                 |              |            |                                    |                                    |
| Test for overall effect: Z = 0.58 (P = 0.56) |            |                 |              |            |                                    |                                    |

Total (95% CI): 52 52 100.0% 0.03 [-0.20, 0.26] Favors [Experimental] Favors [Control]

### Test for subgroup differences: Chi2 = 3.86, df = 2 (p = 0.06); I2 = 0%

Contd...
### Table

| Study or Subgroup | Experimental Mean | Control Mean | Mean Difference | Mean Difference |
|-------------------|------------------|--------------|----------------|----------------|
|                   | SD Total | Mean | SD | Total | Weight IV, Fixed, 95% CI | IV, Fixed, 95% CI |
| 1.5.1 CTG         |          |      |    |       |                           |                |
| Ghairoloudi et al. 2014 | 2.4     | 1.4  | 42  | 22.1 | 892  | 29  | 27.2% | 0.20 [-0.61, 1.01]  |
| Iazif et al. 2016 | 2.14    | 1.3  | 15  | 2.14  | 1.3  | 15  | 20.5% | 0.00 [-0.93, 0.93]  |
| Subtotal (95% CI) | 57      | 47.8% | 11  | 0.11 [-0.50, 0.72] |
| Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0% |
| Test for overall effect: Z = 0.37 (P = 71) |
| 1.5.2 PRF         |          |      |    |       |                           |                |
| Agrawal et al. 2016 | 1.2     | 1.39 | 15  | 1.52  | 1.73 | 15  | 14.1% | -0.32 [-1.44, 0.80] |
| Rehan et al. 2018 | 1.5     | 1.35 | 10  | 1.05  | 10  | 15.8% | 0.50 [-0.56, 1.56] |
| Subtotal (95% CI) | 25      | 29.9% | 11  | 0.11 [-0.66, 0.88] |
| Heterogeneity: Chi² = 1.08, df = 1 (p = 0.30); I² = 8% |
| Test for overall effect Z =0.29 (P = 0.77) |
| 1.5.3 CHORION     |          |      |    |       |                           |                |
| Mahajan et al. 2018 | 2.45    | 0.89 | 12  | 2.2   | 1.19 | 10  | 22.3% | -0.25 [0.64, 1.14] |
| Subtotal (95% CI) | 12      | 22.3% | 11  | 0.14 [-0.28, 0.57] |
| Heterogeneity: Not applicable |
| Test for overall effect Z = 0.55 (P = 0.58) |
| Total (95% CI)    | 94      | 79   | 100% | 0.14 [-0.28, 0.57] |
| Heterogeneity: Chi² = 1.25, df = 4 (P = 0.87); I² = 0% |
| Test for overall effect Z = 0.67 (P = 0.50) |

Favors [experimental] Favors [control]

### Diagram

Figs 2A and F: (A) Forest plot for RD reduction; (B) RW reduction; (C) Forest plot for WKG gain; (D) PD reduction; (E) Forest plot for CAL reduction; (F) GT gain
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