

POSTOPERATIVE MACULAR HOLE FORMATION AFTER VITRECTOMY WITH INTERNAL LIMITING MEMBRANE PEELING FOR THE TREATMENT OF EPIRETINAL MEMBRANE

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Purpose: To evaluate the incidence, clinical features, and outcomes of macular hole formation after pars plana vitrectomy with internal limiting membrane peeling for the management of epiretinal membrane.

Methods: Retrospective consecutive chart review of 423 cases.

Results: Eleven subjects developed postoperative macular holes (incidence 2.6%; 95% confidence interval, 1.5–4.6%). Two of the 11 subjects developed central macular holes (incidence 0.5%; 95% confidence interval, 0.1–1.7%) while 9 had eccentric (nonfoveal) macular holes (incidence 2.1%; 95% confidence interval, 1.1–4.0%). Seven of the 9 eccentric macular holes were <115 μ m in diameter, 7 were determined to be along the margin of the internal limiting membrane peel, and 8 were either in the superior or temporal macula. The two central macular holes were closed with subsequent pars plana vitrectomy and gas tamponade. There was no association between macular hole formation and age, gender, preoperative visual acuity, axial length, and preoperative central macular thickness. Overall, a 0.2 or more improvement in logMAR was associated with pseudophakia and poorer preoperative acuity on univariate and multivariate analysis, whereas increased preoperative central macular thickness was associated with improved outcomes on univariate but not multivariate analysis.

Conclusion: Postoperative macular hole formation is an infrequent sequela to pars plana vitrectomy with internal limiting membrane peeling for epiretinal membrane. In our cohort, eccentric macular holes tended to be small, located along the edge of the internal limiting membrane peel, and were not visually significant.

RETINA 34:890–896, 2014

Pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peeling has become a popular technique for the management of epiretinal membranes (ERMs) during the past decade.^{1–3} Controversy concerning possible iatrogenic retinal damage from this procedure has mainly focused on the use of ILM-staining dyes such as indocyanine green (ICG).^{4–11} However,

postoperative retinal breaks occurring within the macula after PPV with combined ERM/ILM peeling have infrequently been reported,^{12–16} and although comparatively little is known of their incidence, a recent report suggests that these may occur in 2.2% of cases.¹⁴ Postoperative retinal breaks may be located centrally or extrafoveally and may be either full-thickness holes or pseudoholes.¹⁷ Putative mechanisms for hole formation include weakening of the glial structure of the retina induced by the decapitation of Müller cells, opening or deroofting of intraretinal cysts, contraction of residual ILM, direct mechanical trauma, and ILM-staining dye toxicity. Our study addresses the incidence, clinical features, and outcomes of macular hole formation after

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None of the authors have any financial/conflicting interests to disclose.

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PPV with ILM peeling for the treatment of idiopathic ERM.

Methods

This study adhered to the accords of the Declaration of Helsinki and was approved by the Southwest Retina Specialists Institutional Review Board. A 3-surgeon consecutive retrospective case series of patients who underwent PPV with ILM peeling for ERM was undertaken from March 2010 to March 2012. The inclusion criteria were as follows:

1. Patients were 18 years or older.
2. The preoperative Snellen best-corrected visual acuity (BCVA) was between 20/25 and 20/200.
3. The BCVA was considered to be significantly reduced by the presence of an idiopathic ERM.

Exclusion criteria were:

1. Patients lost to follow-up before the 6-month post-surgical examination.
2. The patient had a previous PPV for any indication.
3. Patients had undergone PPV with ILM peeling for primary or recurrent rhegmatogenous retinal detachment with proliferative vitreoretinopathy or tractional retinal detachment.
4. The patient had an ERM with concomitant full-thickness macular hole or vitreomacular traction.
5. The patient had evidence of significant preoperative macular disease (i.e., diabetic macular edema, age-related macular degeneration, etc.).
6. The patient underwent a combined procedure (i.e., cataract surgery) at the same time as PPV or in the postoperative study period.

All patients underwent a standard 3 port 23-gauge or 25-gauge PPV with the Constellation Vision System (Alcon, Fort Worth, TX) and the BIOM Viewing System (Oculus, Wetzlar, Germany) for visualization by 1 of the 3 fellowship-trained vitreoretinal specialists. A posterior vitreous detachment, if not already present, was created using aspiration with the vitrectomy hand-piece or extrusion cannula. High-speed vitreous cutting rates (2500–5000 cuts/min) were applied. Indocyanine green -dye assisted membrane peeling and ILM peeling with end-gripping ILM forceps was performed in all cases. Approximately 0.05 mL of ICG (0.05%) was allowed to contact the retinal surface for 30 seconds to 90 seconds before removal. The ILM was removed from the macula between the superior and inferior arcades and at least one disk diameter temporal to the fovea. The peripheral retina was inspected and any retinal degeneration or peripheral retinal tears were treated with endolaser photocoagulation or cryotherapy according to

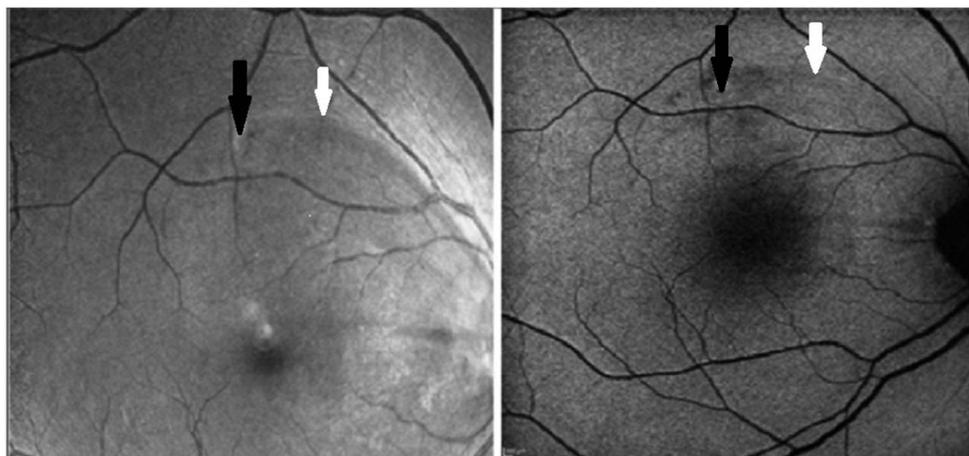
surgeon preference. At the completion of the case, vitreous substitution with fluid, air, or gas was left to the surgeon's discretion.

The data collected included preoperative BCVA, postoperative BCVA at 6 months of follow-up, the preoperative central macular thickness (CMT) on spectral domain optical coherence tomography (SD-OCT), lens status (phakic vs. pseudophakic), age, axial length, and gender. The data collected on those subjects who developed a postoperative macular hole included macular hole diameter, macular hole location, time interval for the formation of the macular hole, the type of postoperative vitreous substitute used, and whether or not a secondary PPV was performed as a result of the macular hole. Heidelberg Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany) scans were inspected in each case to determine the presence of a postoperative macular hole at 2 weeks, 6 weeks, and 6 months. All areas between the superior and inferior arcades of the macula were examined for macular hole formation. Only full-thickness retinal defects were considered as macular holes (i.e., not partial-thickness holes). Heidelberg Spectralis autofluorescence, red-free, and OCT images were used to determine the edge of the peeled ILM and the location of the macular hole regarding the peeled ILM. The size of each macular hole was determined by the measuring software of the Heidelberg Spectralis OCT. For the purpose of analysis, Snellen BCVA was converted to logMAR values.¹⁸ We searched for possible associations of macular hole formation by performing univariate logistic regression and multivariate logistic regression using all of the key variables recorded. Additionally, we examined for possible predictors for favorable functional outcomes (defined as an improvement of 0.2 LogMAR or more) using both univariate and multivariate logistic regression. Statistical analysis was performed using the AcaStat version 8.1.4 statistical package (AcaStat, 8.1.4 ed. Leesburg, VA). Tests of significance were 2-tailed and a $P < 0.05$ was considered statistically significant. Correction for multiple comparisons was made using the False Discovery Rate (FDR) online calculator¹⁹ that uses the false discovery method of Benjamini and Hochberg.²⁰

Results

Four hundred and twenty-three cases met the enrollment criteria; of these, 11 cases (incidence 2.6%; 95% confidence interval [CI], 1.5–4.6%) developed a macular hole in the postoperative period. Two of the 11 cases developed a central macular hole (incidence 0.5%; 95% CI, 0.1–1.7%) while 9 had eccentric (nonfoveal) macular hole formation (incidence 2.1%; 95% CI,

Fig. 1. The red-free (right) and autofluorescence (left) images in Subject 2 displaying the postoperative eccentric macular hole development (black arrow) along the superior margin of the ILM peel (white arrow).



1.1–4.0%) (Figures 1 and 2). The average macular hole diameter was $144.5 \mu\text{m}$ (95% CI, $85.4\text{--}203.6 \mu\text{m}$) and the average time for detection was 4.2 weeks (95% CI, 2.8–5.6 weeks). Each of the two cases with postoperative central macular hole formation underwent a secondary PPV with sulphur hexafluoride (SF_6) gas tamponade and 3-day face down positioning within 3 weeks of the postoperative macular hole diagnosis. Subject 9 was found to have residual ILM at the margin of the central macular hole after ICG staining. Further ILM removal was performed on Subject 9. No residual ILM was found in Subject 5 after ICG staining, and thus no additional peeling was performed. The central macular hole in both subjects was determined to be closed within 1 month of the secondary PPV (Figure 3). None of the cases with eccentric macular hole required surgical intervention in the postoperative period. Table 1 summarizes the clinical characteristics of the macular holes encountered in this study.

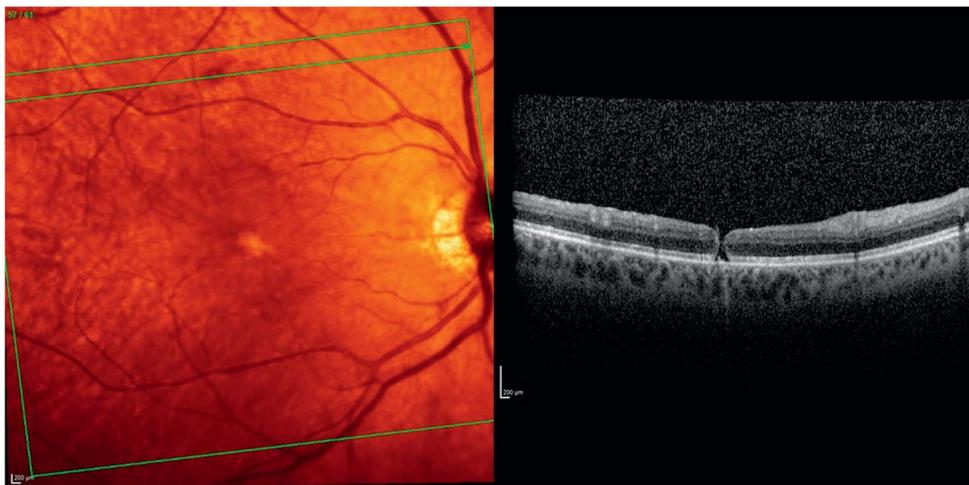
Analysis of our data does not suggest a correlation between the likelihood of macular hole formation and

age, preoperative BCVA, preoperative CMT on SD-OCT, phakic status, gender, or axial length (Table 2). In terms of favorable functional outcomes, there was an association with pseudophakic status and poorer baseline visual acuity on both univariate and multivariate logistic regression analysis (Table 3); an association between a favorable functional outcome and increased preoperative CMT was also found on univariate but not multivariate analysis.

Discussion

The safety of ILM peeling remains a controversy in macular surgery, although randomized controlled studies suggest improved outcomes for macular hole closure when ILM peeling is combined with vitrectomy,^{21,22} such a benefit has not yet been clearly demonstrated for the management of ERM.¹ Furthermore, a few studies have described the formation of postoperative macular holes after ILM peeling for ERM.

Fig. 2. The SD-OCT image in Subject 2 displaying the postoperative eccentric full-thickness macular hole.



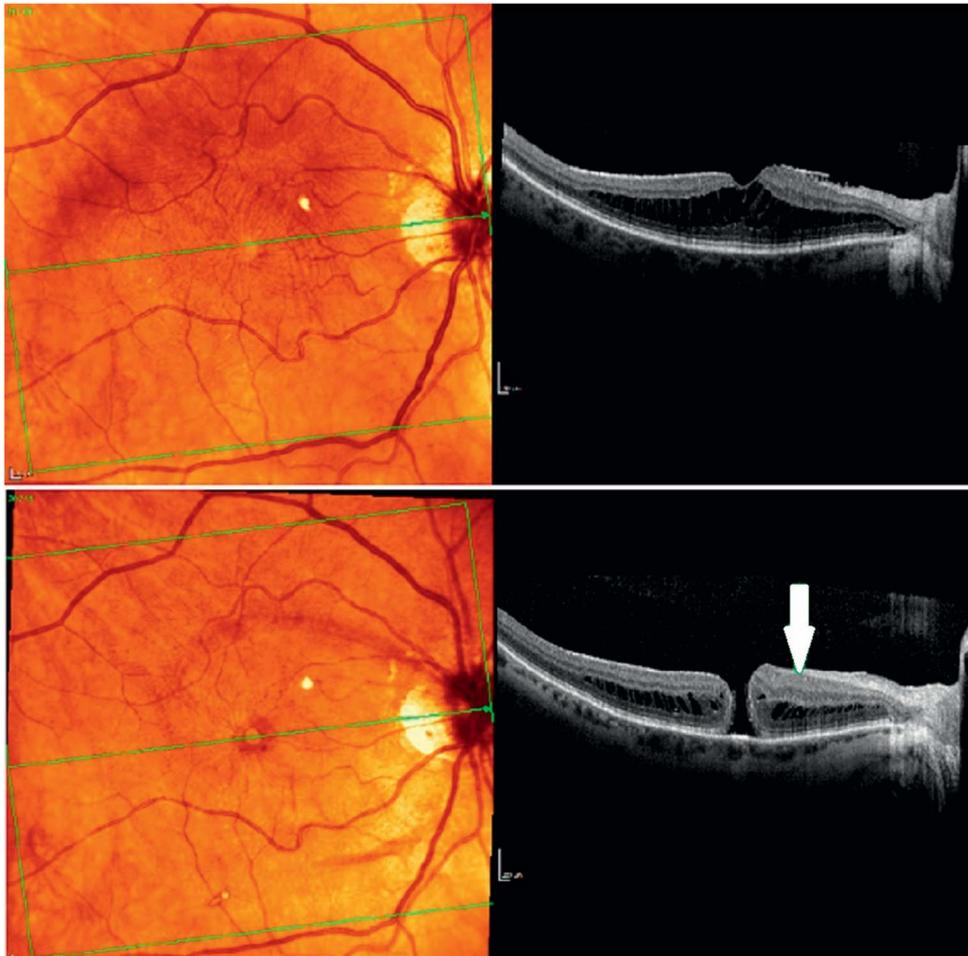


Fig. 3. The SD-OCT images of Subject 9 demonstrating the preoperative ERM with secondary CME (top), and the postoperative central macular hole that developed after ERM/ILM removal (bottom). The arrow marks residual ILM at the margin of the macular hole.

Recently, Sandali et al¹⁴ reported on 509 patients who underwent PPV with membrane peeling for ERM. The ILM was peeled in just 64.4% of their cases. Five extrafoveal (0.98%) and 6 central (1.2%) macular holes developed in the postoperative period in their study. Four of the 5 patients with extrafoveal macular holes had undergone ILM peeling, but none of the

cases in which ICG was used developed postoperative macular holes (however, only 32 cases in their study used ICG during the surgery). Although it is difficult to compare the results of our study with those of Sandali et al,¹⁴ since over one third of their patients did not have the ILM peeled and only a small fraction were exposed to ICG during the surgery, the overall

Table 1. Characteristics of Eyes With Macular Hole Formation

Patient	Preoperative VA	Postoperative VA	Lens Status	Hole Diameter, μm	Location	Adjacent to Peel Junction?	Time Noted, weeks	Preoperative OCT CMT, μm	Further TPPV
1	0.4	0.4	Phakic	97	Superior	Yes	2	392	No
2	0.5	0.4	Pseudophakic	68	Superior	Yes	6	434	No
3	0.4	0.2	Pseudophakic	88	Superior	Yes	2	367	No
4	0.3	0.2	Phakic	82	Inferior	Yes	2	350	No
5	0.5	0.4	Phakic	245	Central	No	2	485	Yes
6	0.3	0.1	Pseudophakic	76	Temporal	Indeterminate	6	341	No
7	0.6	0.4	Pseudophakic	267	Temporal	Yes	2	438	No
8	0.5	0.5	Phakic	112	Superior	Indeterminate	6	417	No
9	0.6	0.4	Pseudophakic	276	Central	No	6	522	Yes
10	0.5	0.4	Pseudophakic	223	Temporal	Yes	6	359	No
11	0.4	0.3	Pseudophakic	56	Superior	Yes	6	374	No

Table 2. Comparison of Preoperative Characteristics Between Patients Developing Postoperative Macular Holes and Those not Developing Macular Holes

Variable	No Macular Hole	Macular Hole	Univariate <i>P</i>	Multivariate <i>P</i>
Age, years	67.8 (67.0–68.6)	66.7 (62.8–70.6)	0.68	0.49
Female:male	208:204	6:5	0.79	0.93
Presenting acuity, logMAR	0.44 (0.43–0.45)	0.45 (0.38–0.52)	0.77	0.77
Phakic:pseudophakic	181:231	4:7	0.62	0.58
Axial length, mm	23.2 (23.0–23.4)	23.2 (22.6–23.8)	0.94	0.96
Preoperative OCT macular thickness, μm	410.2 (405.0–415.2)	407.2 (368.1–446.3)	0.83	0.63

incidence of macular hole formation is similar. The results of our study, however, showed fewer instances of central macular holes and a higher incidence of eccentric macular holes compared with Sandali et al.¹⁴

Patients with postoperative noncentral macular holes in our study were visually asymptomatic, this finding is in keeping with previous reports.^{12,13,15,16,23} Eccentric macular holes seem to have minimal impact on the patient's subjective visual function unless they occur either close to the fovea (within one disk diameter) or in the nasal macula within the papillomacular bundle. Furthermore, they do not seem to readily accumulate subretinal fluid with subsequent detachment, though like other macular holes, there may be a small risk of detachment in certain patients (e.g., high myopes). In keeping with previous descriptions, most of the eccentric macular holes occurred either in the superior or temporal macula.^{12,13,15,16,23}

Excluding the two central macular holes, seven of the nine eccentric macular holes in this study appeared to be intimately related to the margin of the ILM peel (the ILM peel margin could not be definitively determined in the other two cases, although these macular holes were in a location that might have been along the ILM peel margin). This finding suggests that eccentric macular holes may be caused either by contraction of the ILM as suggested by Mason et al,¹² by the shear stress inherent at the edge of the residual ILM caused

by its thin film characteristics,²⁴ or alternatively through the effects of forces active in the area adjacent to the ILM margin during peeling itself.²⁵

Steven et al¹⁵ favored the hypothesis that ILM peeling may traumatize Müller cells sufficiently to cause their degeneration and possible delayed degeneration of adjacent retinal neurons, thereby resulting in postoperative macular hole formation. Indeed, ultrastructural studies have demonstrated Müller cell processes attached to sectioned ILM remnants,²⁶ and ultrastructural analysis of postmortem specimens suggests that ILM peeling causes substantial trauma to Müller cell endfeet.²⁵ If glial structural weakening occurs in the macula, full-thickness retinal holes might develop. This mechanism may account for cases in which macular holes form in areas distinctly clear of the ILM peel margin, and it may also play a role in the formation of holes adjacent to the ILM peel.

Another plausible explanation of eccentric macular hole formation could be iatrogenic forceps trauma during ERM or ILM peeling.¹⁵ In this study, none of the operative reports or postoperative notes was wholly consistent with this mechanism as there were no overt signs of retinal trauma evident during surgery, such as blanching or hemorrhage. However, this mechanism could clearly be important in the genesis of certain types of postoperative macular holes.

Table 3. Comparison of Clinical Characteristics Between the Patients Gaining 0.2 logMAR And Those not Gaining

Variable	<0.2 logMAR Gain (95% CI)	Gain of \geq 0.2 logMAR (95% CI)	Univariate <i>P</i>	Multivariate <i>P</i>
Age, years	67.9 (66.9–68.9)	67.6 (66.2–69.0)	0.77	0.35
Female	139	75	0.66	0.48
Male	140	69		
Presenting acuity, logMAR	0.41 (0.40–0.42)	0.51 (0.49–0.53)	<0.001	0.003
No macular hole	272	140	0.87	0.84
Macular hole	7	4		
Phakic	172	13	<0.001	<0.001
Pseudophakic	107	131		
Axial length, mm	23.2 (23.0–23.4)	23.2 (23.0–23.4)	0.67	0.62
Preoperative OCT macular thickness, μm	400.1 (394.0–406.2)	428.7 (420.1–437.3)	<0.001	0.89

Finally, ICG toxicity may be a contributing cause for these retinal defects. Indocyanine green has been reported to induce retinal pigment epithelium degeneration and photoreceptor toxicity in both human and animal models.^{4–11} However, both eccentric and central postoperative macular holes have been reported to occur without intraocular dye use and when nonretinotoxic dyes were used.^{14–16} In fact, none of the 6 cases that developed postoperative eccentric macular holes in the study by Sandali et al¹⁴ used ICG during the surgery. These observations seem to suggest that ICG toxicity is not the mechanism of macular hole formation.

The two cases of central macular hole in this study were discovered at different follow-up times. Subject 9 had residual ILM at the margin of the central macular hole, with the hole developing sometime between 2 weeks and 6 weeks after surgery. Subject 5 developed the central macular hole sometime in the first 2 weeks after surgery and was not found to have residual ILM at the margin of the hole. Certainly, postoperative contracture of residual ILM may be an important cause of central macular hole formation but this mechanism is unlikely to account for the formation of the central macular hole in subject 5.

Interestingly, the two patients that developed central macular holes in this study had much greater preoperative CMT on SD-OCT compared with the preoperative CMT of the cases without postoperative macular holes and the eccentric macular hole group. Cystic macular edema (CME) was also present on SD-OCT in these two patients. Steven et al¹⁵ reported that four of the six patients with postoperative eccentric macular holes after ILM peeling had CME in their study. It has been suggested that ILM peeling may lead to macular hole formation through the deroofing of intraretinal cysts.¹⁵ However, only one of the cases that developed a postoperative eccentric macular hole in this study had preoperative CME, suggesting that CME cannot account for the formation of all types of postoperative macular holes. A larger set of postoperative central macular holes would need to be evaluated to determine if higher preoperative CMT on SD-OCT or preoperative CME increases the risk for postoperative central macular hole formation.

We found no association between macular hole formation and patient age, gender, preoperative BCVA, preoperative CMT on SD-OCT, axial length, and phakic status. The likelihood of achieving 0.2 or more logMAR improvement in acuity was associated with pseudophakia and worse presenting acuities on both univariate and multivariate analysis. The finding of an increased likelihood of a 0.2 or more logMAR improvement in acuity is in keeping with previous observational studies, which suggests that those with

poorer acuities gain the most number of lines postoperatively.²⁷ It is also anticipated that pseudophakic patients should achieve superior functional outcomes by virtue of the fact that PPV is cataractogenic. We also found that increased preoperative CMT on SD-OCT was associated with favorable function outcomes on univariate but not multivariate analysis.

Our study was limited by its retrospective nature and the fact that there were few central macular holes, thereby making it impossible to identify precisely the factors associated with their formation. One of the strengths of our study is that it used SD-OCT to detect eccentric macular holes: the majority of previous studies used time domain OCT (TD-OCT) to assess macular structure, which may be less sensitive in detecting extrafoveal macular holes.^{13,15,23} Spectral domain OCTs such as the Heidelberg Spectralis are ideal for detecting eccentric macular holes because of their ability to rapidly generate a large number of detailed scans between the vascular arcades in a short amount of time. We believe that small eccentric macular holes have a greater chance of going undetected with TD-OCT, and that this may have hitherto resulted in an underreporting of their true incidence.

In conclusion, the eccentric macular holes occurring in our group of patients were small (7 of 9 were <115 μm), more than one disk diameter from the center of the macula and usually occurred along the superior arcade at the edge of the ILM peel. Given the small size of most eccentric postoperative macular holes and the fact that they are by and large asymptomatic, it is possible that they have been underreported previously. The etiology of eccentric macular hole formation in this study is most consistent with contraction of the remaining edge of ILM or induced shear stress along the margin of the ILM either at, or after, the time of peeling, resulting in expansion of a previously undetectable retinal defect of the type reported in the histopathologic study of Wolf et al.²⁵ However, we cannot definitively exclude the possibility of other mechanisms providing a contribution to the macular holes that we observed. Indeed, several other plausible explanations remain for the development of postoperative eccentric macular holes after ILM peeling, and the empirical evidence does not yet support a consensus explanation.

Key words: postoperative macular hole, epiretinal membrane, pars plana vitrectomy.

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