

Idiopathic vitreomacular traction and macular hole: a comprehensive review of pathophysiology, diagnosis, and treatment

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REVIEW

Abstract

Posterior vitreous detachment (PVD) is a common phenomenon in the aging eye. However, this may be complicated by persistent symptomatic vitreomacular adhesions that exert tractional forces on the macula (vitreomacular traction; VMT). VMT itself may be associated with epiretinal membrane formation and the development of idiopathic macular holes (IMH). Such pathologies may cause visual disturbances, including metamorphopsia, photopsia, blurred vision, and decreased visual acuity, which impact an individual's quality of life. Technologies such as optical coherence tomography allow an increasingly more accurate visualisation of the macular anatomy, including quantification of macular hole characteristics, and this facilitates treatment decision-making. Pars plana vitrectomy remains the primary treatment option for many patients with VMT or IMH; for the latter, peeling of the inner limiting membrane (ILM) of the retina has shown improved outcomes when compared with no ILM peeling. The development of narrow-gauge transconjunctival vitrectomy systems has improved the rate of visual recovery following surgery. Ocriplasmin, by degrading laminin and fibronectin at the vitreoretinal interface, may allow induction of PVD in a non-invasive manner. Indeed, clinical studies have supported its use as an alternative to surgery in certain patient populations. However, further research is still needed with respect to greater understanding

of the pathophysiology underlying the development of VMT and IMH.

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Normal vitreoretinal physiology

The vitreous gel is responsible for the stabilisation of the eyeball; collagen fibres (largely type II) run in an anteroposterior direction through its centre, blending into the anterior vitreous base, and inserting into the posterior vitreous cortex (Figure 1).^{1–4} Spaces between the collagen fibrils are maintained by the protein opticin, and the fibril-associated glycosaminoglycan chondroitin sulphate.^{3,5} These spaces are filled with water (which constitutes >98% of the vitreous gel) and hyaluronic acid.^{1,3,4,6} The vitreous gel is therefore constructed to resist both tractional and compressive forces.⁴ Recently, further interest has been shown in a common feature of normal vitreous known as the posterior precortical vitreous pocket. This was first described by Worst,⁷ and can appear on optical coherence tomography (OCT) as boat-shaped lacunae in the macular region, with a thin posterior vitreous cortex that is thinnest at the fovea.⁸ However, its exact physiological function is unknown.

The interface between the vitreous gel and retina (vitreoretinal interface; VRI) is a complex structure.⁹

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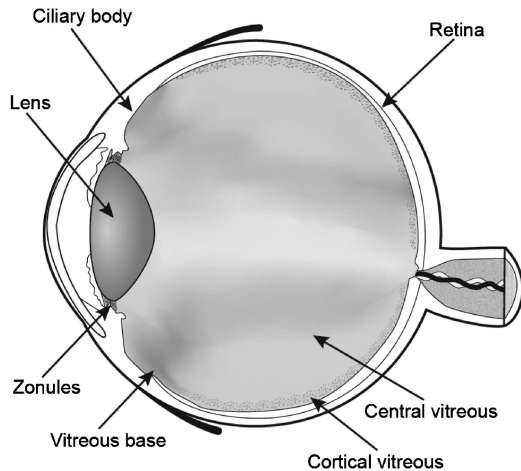


Figure 1 The orientation of collagen fibrils within the vitreous gel (adapted from Le Goff and Bishop⁴). Redrawn with permission from P Bishop, The University of Manchester.

The more densely packed collagen fibrils of the posterior vitreous cortex (which is 100–300 μm in thickness) lie over the macula and are superficially inserted into the internal limiting membrane (ILM) of the retina.^{3,4,10} These are attached by adhesion molecules such as laminin, fibronectin, and heparan sulphate proteoglycans, which interact with opticin in the vitreous gel.^{4,5,11} The vitreous gel itself is most firmly attached to the retina at the vitreous base, optic disc, and fovea, and along the major retinal blood vessels.⁹ In particular, the attachment at the vitreous base is very strong and is generally fixed unless severe blunt trauma occurs. Indeed, the attachment is so tenacious that under such circumstances, the pars plana epithelium also detaches with the vitreous base. Conversely, it is possible to separate attachments at the optic disc, fovea, and retinal blood vessels surgically in most cases albeit with difficulty in younger patients.

Normal aging is accompanied by a number of physiological changes in the vitreous gel. After the age of 40, it undergoes progressive liquefaction (synchysis), with fluid escaping through defects in the posterior vitreous cortex, eg, those at the optic disc or prepapillary hole.^{3,4} This results in the development of fluid-filled pockets, which generally begin in front of the macula, enlarging the premacular vitreous pocket but also in the central vitreous cavity.⁶ Typically by the age of 80 years, around 50% of the vitreous gel has been liquefied.^{4,6} This corresponds with a simultaneous decrease in gel volume and a lateral aggregation of the collagen fibrils.³ Over time, the fluid-filled pockets coalesce and enlarge, and a gradual destruction of the collagen-hyaluronate network occurs, resulting in a weakened adhesion between the vitreous and retina.^{2,4} This leads to the eventual development of a shallow localised separation of the vitreous gel from the perifoveal area of the retina, which progresses over time

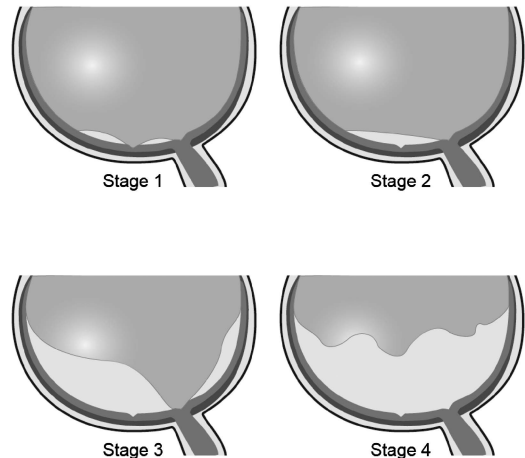


Figure 2 Stages of posterior vitreous detachment (PVD) during healthy aging (adapted from Johnson;² Uchino *et al*¹²). Stage 1, perifoveal vitreous detachment with residual vitreofoveal adhesion; Stage 2, perifoveal vitreous detachment with persistent attachment to the optic disc but without vitreofoveal adhesion; Stage 3, near-complete PVD with only vitreopapillary adhesion remaining; Stage 4, complete PVD.

(Figure 2).^{2,12} Finally, total collapse of the collagen fibrils (synaeresis) leads to complete detachment of the posterior vitreous from the retina, and the vitreous gel now occupies an anterior position in the vitreous cavity.^{3,6}

This process occurs over several months or years.² In many cases, the process of posterior vitreous detachment (PVD) is asymptomatic, until vitreous separation from the optic disc occurs.² Symptoms of complete (acute) PVD include light flashes and floaters. Light flashes are caused by vitreous traction on the peripheral retina, while floaters may be due to blood, condensations of vitreous collagen, or glial tissue torn from the optic nerve.¹³

Studies in healthy adults with otherwise normal eyes have shown that focal perifoveal PVD occurs in around 50% at ages 30–39 years, whereas complete PVD is observed in 50% or more of individuals aged 70 years or older.^{12,14–16} PVD is significantly more common in postmenopausal women than men; this is thought to be due to the effects of decreased oestrogen on connective tissues such as those within the vitreous gel.^{6,17} The presence of myopia is also associated with a three- to fourfold increased risk of PVD compared with absence of myopia.¹⁷

Pathophysiology of vitreomacular traction and macular hole

Vitreomacular traction

Normal age-related PVD may be complicated by persistent vitreomacular adhesions (VMA) between the vitreous cortex and the macular area following synaeresis.^{2,9,18} Such adhesions can be focal or broad,

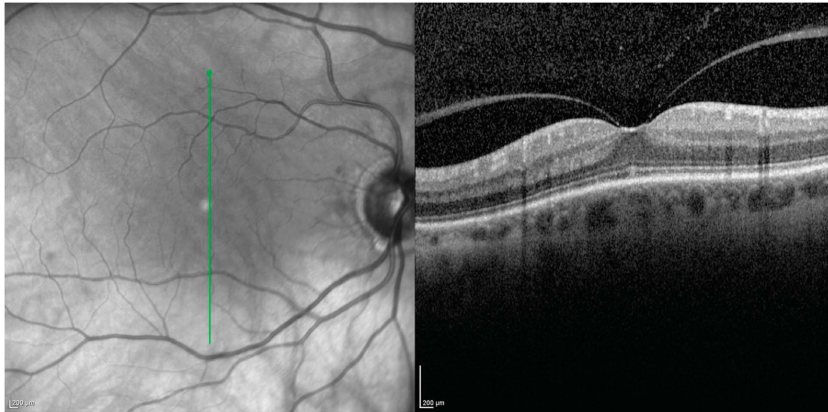


Figure 3 Central foveal vitreomacular adhesion without traction. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

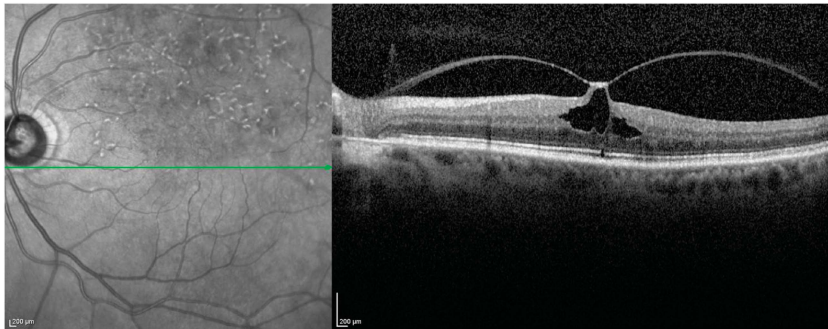


Figure 4 Vitreomacular traction with retinal cavitation. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

encompassing the foveola only, or a wider region of the macular area and the optic disc.^{19,20} Simple (asymptomatic) VMA is not associated with structural distortion of the macular architecture (Figure 3). However, such adhesions may exert tractional forces on the macula (vitreomacular traction; VMT), increased during ocular saccades, causing retinal distortion and disruption.¹⁸ Increasing width of the VMA is associated with a decreased tractional force and therefore reduced foveal deformation. For example, the smallest adhesions at the fovea may result in focal inner retinal cavitation (foveal cyst) (Figure 4), while larger vitreoretinal adhesions ($\geq 1500 \mu\text{m}$) can lead to more generalised foveal profile flattening (ie, a loss of foveal depression) and detachment.^{20–22} VMA and VMT may be differentiated by clinical symptoms (chiefly, visual loss, blurred vision, and metamorphopsia) and with OCT.² However, some cases of VMT may not demonstrate obvious deleterious effects on vision.

In many VMT cases, an epiretinal membrane (ERM; 10–20 μm in thickness) develops during the early perifoveal stages of PVD (Figure 5).^{2,23} Histologically, two

types of ERM can be observed; a simple or type 2 ERM growing directly on the ILM composed of a monolayer of retinal glial cells producing type IV collagen—retinal pigment epithelial (RPE), fibroblastic, and inflammatory cells are absent; and a more complex or type 1 ERM sometimes containing cells such as fibrous astrocytes, myofibroblasts, fibrocytes, macrophages, and RPE cells, in addition to glial cells.^{23–27} Multilayered sheets of cells can be seen and are separated from the ILM by a layer of native vitreous (type II) collagen remaining after incomplete PVD (Figure 6).^{23,26,27} Growth factors within the VRI may contribute to fibrocellular proliferation.²⁷ The native collagen is thought to facilitate the proliferation of ERM by acting as a scaffold.^{23,28} The corresponding side of the split and detached vitreous cortex, forming the outer surface of the ‘cone’, also acts as a scaffold and thus cellular proliferation occurs along both sides of this aberrant VRI and is thought to contribute to the tenacity of VMA in VMT (Figure 7).^{20,23}

The presence and type of ERM also contributes to the morphological alterations observed at the VRI. Simple (non-contractile) ERM is associated with retinal surface wrinkling ‘cellophane’ maculopathy (an irregular

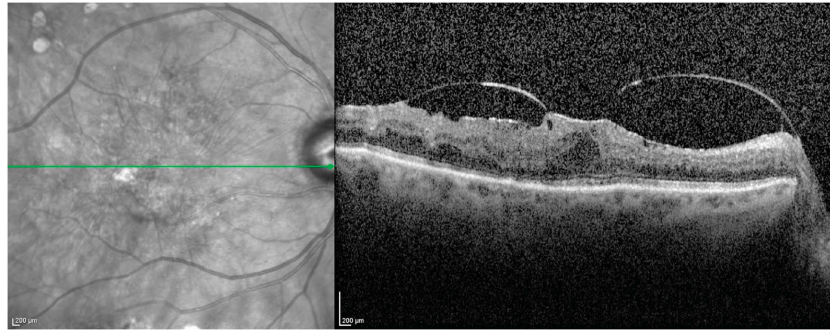


Figure 5 Vitreomacular traction with epiretinal membrane. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

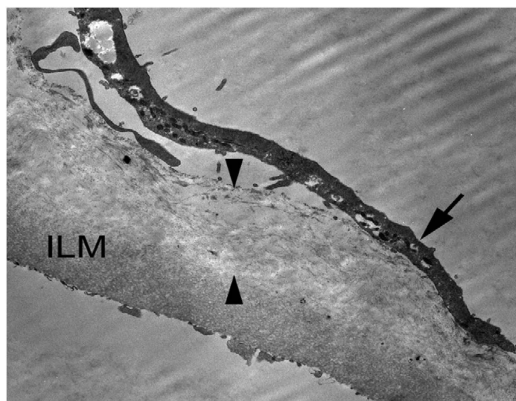


Figure 6 Fibrous epiretinal membrane visualised using transmission electron microscopy. Collagen fibrils (between the arrowheads) situated between the inner limiting membrane of the retina and a layer of fibrocytes (shown by the arrow). The layer of collagen fibrils is ~10 nm in thickness. Reproduced with permission from R Spaide, Vitreous-Retina-Macula Consultants of New York, New York, USA.

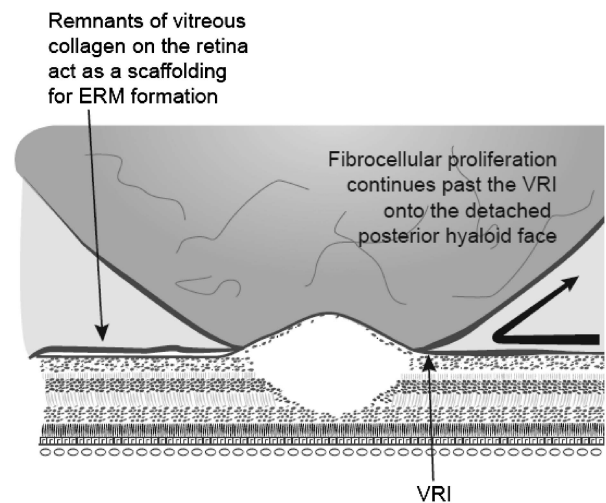


Figure 7 Complex epiretinal membrane formation (adapted from Chang *et al*²³). VRI, vitreoretinal interface. Reproduced with permission from R Spaide, Vitreous-Retina-Macula Consultants of New York, New York, USA.

glistening) observed on light reflex with no distortion of the inner retina.^{23,29} However, the contraction of myofibroblasts within the more complex type of ERM has been proposed to exert a tangential traction at the VRI, which can result in retinal puckering, thickening, folding, or detachment, together with vascular distortion.^{27,29-31} Contraction of complex ERM can therefore exert profound effects on vision²⁹ and significantly increase the effect of any VMA. VMT and any associated ERM can also be associated with changes in the retinal vasculature.⁹ As the retina is pulled apart, there is a reduction in interstitial fluid pressure, with subsequent fluid influx from the retinal vasculature (ie, leakage of blood) and cells, leading to macular oedema.¹⁸

Although outside the scope of this review, a meta-analysis has estimated that VMA (including VMT) is found in a reported 23% of eyes in patients with exudative (wet) age-related macular degeneration

(AMD) and often the area of adherence corresponds to the area of choroidal neovascularisation.³² The nature of this relationship is unclear and its aetiological significance uncertain. It may represent a secondary phenomenon although still exacerbate disease course and response to treatment.

Similarly, the relationship between VMT and diabetic macular oedema (DMO) has also been examined. In the recent meta-analysis conducted by Jackson *et al*,³² it was estimated that VMT (and ERM with traction) was present in 29% of DMO cases scheduled for surgery. Individual studies have estimated the prevalence of any type of epimacular traction including both epiretinal membrane, vitreoschisis with a splitting of the vitreous cortex termed vitreoschisis, and classic VMT occurring overall in 24-32% of eyes with DMO.^{33,34} The presence of asymptomatic VMA has been reported to increase the risk of diffuse DMO by more than threefold when compared with diabetic patients demonstrating complete PVD or

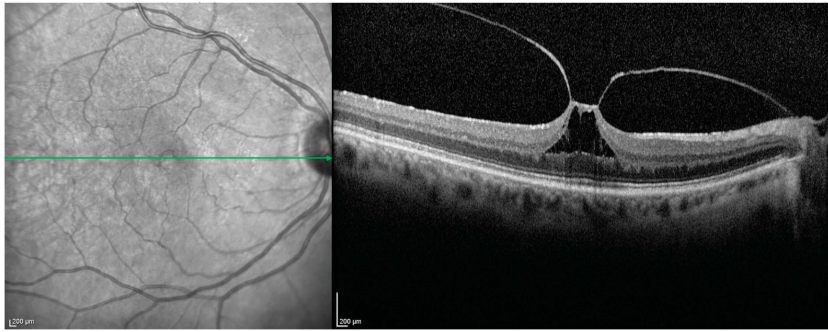


Figure 8 Vitreomacular traction with pseudocyst. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

complete vitreoretinal attachment.³⁵ Asymptomatic VMA is also associated with a significantly reduced likelihood of spontaneous DMO resolution relative to patients whose eyes demonstrate complete PVD.³⁶ Type 2 ERMs are common with VMT in patients with tractional DMO.³⁷

Macular hole

Idiopathic macular holes (IMHs) are round full-thickness vertical retinal defects in the foveal neurosensory retina.^{31,38} Gass hypothesised that IMHs begin with tangential traction of the prefoveal vitreous cortex, which results in a foveal dehiscence that progresses from foveolar detachment to a full-thickness IMH.^{39,40} However, more recent research (using ultrasound and OCT) has elucidated that IMHs are initiated during perifoveal PVD as a consequence of anteroposterior and dynamic VMT.^{41–43}

The anterior tractional forces acting at the foveola firstly produce an intrafoveal split, which evolves into a foveal pseudocyst (Figure 8).^{21,44,45} The pseudocyst may then become extended, disrupting and separating the outer retinal layer while raising the inner retinal layer (Figure 9).^{38,44,45} Degeneration of the retinal tissue secondary to these tractional forces at the foveola may facilitate this process.

Dehiscence of the foveal cyst creates a full-thickness defect, including the inner/outer segment (IS/OS) junction of the photoreceptor layer.^{38,44,46} Complete detachment of the cyst roof can be observed by the appearance of an operculum within the vitreous gel, which consists of glial tissue and hyperplastic Müller cells from the inner retinal surface, as well as components of the outer retina including cone cells in up to 65% of cases (Figure 10).^{38,43,47}

Before the creation of a full-thickness retinal defect, the evolving macular hole corresponds to Gass's stage 1. A stage 2 hole is a full-thickness defect less than 400 μm in width and a stage 3 hole greater than 400 μm in width.



Figure 9 Vitreomacular traction with inner retinal cystic change and outer retinal detachment. Reproduced with permission from DH Steel.

Stage 4 refers to the situation when the vitreous separates over the entire posterior retina, including the optic disc, with a Weiss ring observed fundoscopically.^{38,40} In total, ~55% of patients presenting with IMH exhibit VMT to the edges of the IMH, with 67% of stage 2 holes having VMT (Figure 11), but very few with stage 3 IMH having persistent VMT.³⁸ Conversely, some stage 4 holes can be less than 400 μm in size.

A small early IMH has the capacity to repair itself after complete VRI separation via proliferation of retinal glial cells.⁴³ Paradoxically, if this repair mechanism fails, glial cells migrating to the edge of the hole can progressively contract, resulting in its enlargement. The edge of the IMH subsequently becomes progressively elevated by a cuff of subretinal fluid that may be accompanied by thickening of the neurosensory retinal tissue (Figure 12).^{48,49}

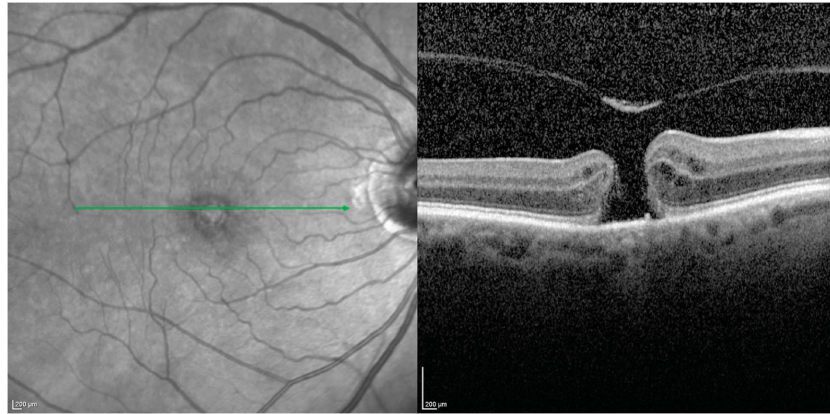


Figure 10 Idiopathic macular hole with operculum. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

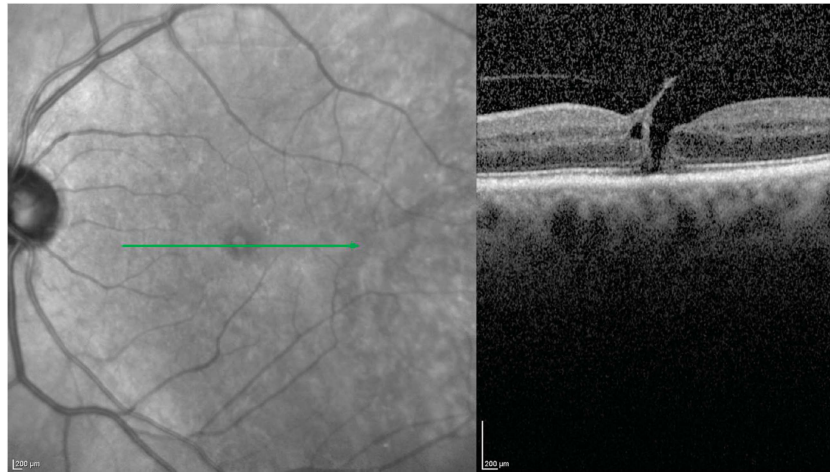


Figure 11 Small idiopathic macular hole with vitreomacular attachment. Left, fundus photography; right, optical coherence tomography (OCT); Green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

Lamellar macular holes are formed by the same process as full-thickness IMH with the exception that the photoreceptor layer remains intact.^{45,50,51} On OCT, an irregular defect in the inner retina is seen, with an intact outer retina and a near-normal perifoveal retinal thickness (Figure 13a).⁵² Macular pseudoholes (Figure 13b) are fundoscopically apparent holes ERM that is associated with a thickened but intact neurosensory retina and are often associated with good vision. They are characterised by a steep foveal pit of a small diameter, with thickened foveal edges.⁵² However, a mixed appearance may also be seen (Figure 13c).

A variety of traumatic events including blunt trauma, phototoxicity, spontaneously resolved VMT/IMH and other unrecognised causes can cause localised outer retinal defects, which appear as tiny (50 – 100 µm) apparent foveal microholes.⁵³ The inner retina remains

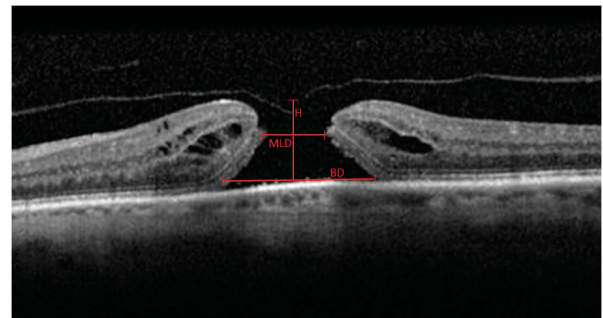


Figure 12 Macular hole with elevated cuff. H, height; MLD, minimum linear diameter; BD, base diameter. Macular hole index (MHI) = height (H)/base diameter (BD). Reproduced with permission from DH Steel.

intact and the condition is non-progressive, occurring in patients of all ages. The visual acuity is often good although the patient may be aware of a central scotoma.⁵³

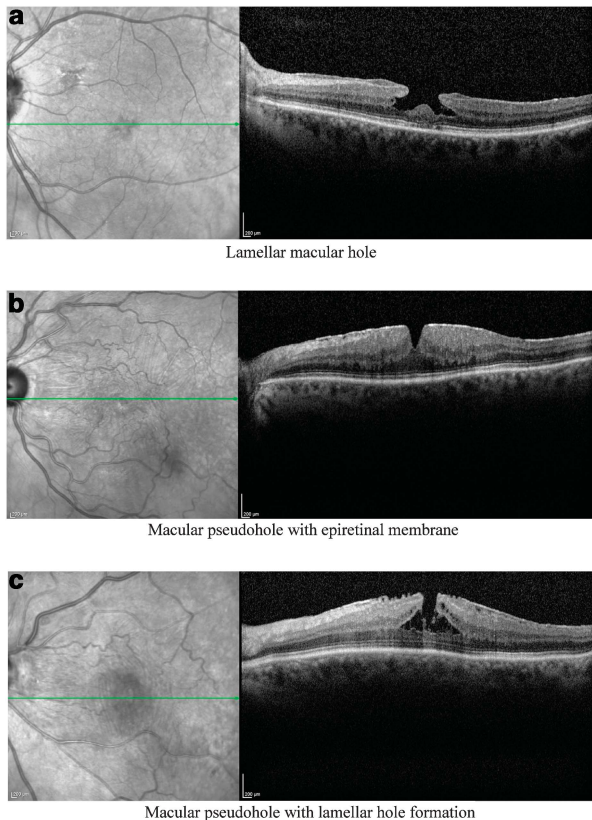


Figure 13 Lamellar macular hole and macular pseudohole. (a) Lamellar macular hole. (b) Macular pseudohole with epiretinal membrane. (c) Macular pseudohole with lamellar hole formation. Left, fundus photography; right, optical coherence tomography (OCT); green line corresponds with level of OCT image. Reproduced with permission from DH Steel.

Risk factors and epidemiology

Few studies have specifically investigated the epidemiology of idiopathic VMT, due to its overlap with many other ocular disorders and abnormalities. However, it has been estimated that the prevalence of VMT in isolation from IMH is ~22.5 per 100 000 of the general population, while the incidence is estimated as 0.6/100 000 per year.⁵⁴ In observational and interventional studies, the mean age of patients diagnosed with VMT is around 65–75 years (range ~48–83 years), with a predominance of females.^{2,19,20,23,26}

IMH predominantly occurs in individuals aged >65 years.^{9,42,55,56} The prevalence of IMH has been estimated at around 0.1–0.8% of adults aged >40 years,^{57–61} while the age-adjusted incidence has been reported as 7.8 per 100 000 of the general population per year.⁵⁶ Approximately two-thirds of patients are women and the condition is unilateral in around 80% of cases.^{42,55,56} A number of factors have been suggested to increase the risk of IMH development, such as elevated plasma fibrinogen,⁶² while in women, use of oestrogen-replacement

therapy is associated with a reduced risk of IMH. In individuals with severe myopia (–14 to –32 dioptres), the prevalence of IMH has been reported to be as high as 6%.⁶³ Notably, the risk of IMH development in fellow eyes without manifest vitreous separation has been estimated at around 7–12% after 5 years and 17% at 10 years.^{55,64}

Assessment and diagnosis

Symptoms at presentation

The cardinal symptoms of VMT are related to the structural macular changes associated with the condition and include decreased visual acuity (VA), metamorphopsia, micropsia (a diminution of objects within the visual field), and rarely photopsia (luminous rays or flashes).^{2,18,31} However, even in patients with visible VMT, symptoms may be absent. The impact of age-related eye disease (including IMH) on quality of life is substantial. Impairments in physical activity, engaging in close activities, and decreased social interaction, as well as emotional effects have been reported.⁶⁵ Vision-dependent activities such as reading small print, reading road signs, and driving at night can all be affected.^{65,66}

Most stage 1 and many stage 2 IMHs are asymptomatic, especially if the other eye is normal and the non-dominant eye affected.⁶⁷ However, late-stage IMHs are associated with significantly reduced VA, metamorphopsia, and loss of central vision with a central scotoma, usually resulting in severe visual impairment.^{9,55,58} VA is inversely correlated with the size of the IMH.⁵⁵

Diagnostic tools

As a first step in patients with suspected VMT/IMH, a thorough history needs to be taken, which should include the duration and type of symptoms, ophthalmological history (glaucoma or other disorders, traumatic injuries, surgery, or other treatments), and the use of medications that are potentially related to the development of macular cysts (eg, systemic niacin, topical prostaglandin analogues).^{68,69}

There are a number of technologies that allow visualisation of the vitreous and retina that can aid the identification and characterisation of VMT and/or IMH; these allow differentiation from other fundoscopically similar disorders such as central serous retinopathy, subfoveolar drusen, and solar maculopathy.^{68,69} Visualisation of the fundus should include the peripheral retina to exclude pathology such as retinal tears and vascular lesions.⁷⁰ Fundus photography and in particular red-free or blue-reflectance imaging can highlight the presence of ERM associated with vascular distortion, and also ERM with macular pseudohole.² Fundoscopically,

IMH may exhibit some or all of the following: fine, drusen-like yellow deposits in the base of the hole, a surrounding cuff of subretinal fluid, a distinct circular margin around the hole, and an operculum (viewed as a small round opacity suspended within the vitreous gel over the fovea).⁷⁰ A complete PVD is characterised by a mobile prepapillary Weiss ring, which is associated with a faintly visible posterior hyaloid membrane and an optically empty subhyaloid space. However, fundus examination does not identify localised shallow (ie, early, asymptomatic) PVD without posterior vitreous cortex thickening and cannot detect translucent adhesions of the vitreous gel at the macula.

Dynamic B-scan ultrasound permits visualisation of the early stages of PVD and also the presence of an operculum.² It can facilitate differentiation of IMH from idiopathic macular pucker caused by ERM (which characteristically exhibits a complete PVD and Weiss ring).⁷¹ However, it provides relatively low-resolution images relative to OCT.

OCT remains the most accurate method for visualising the VRI and identifying VMT and/or IMH.^{31,72} Within the last few years, spectral domain OCT (SD-OCT) has become more widely available, providing even higher-resolution images (axial resolutions of a little as 5 μm) and reducing artefacts produced by the moving parts of conventional OCT.⁷³ This improved technology can therefore provide detailed visualisation of VMT and/or ERM (Figure 5), retinal distortion, and macular detachment.^{19,20,22} This includes the accurate quantification of vitreous adhesions (horizontal and vertical) and foveal cavitation in patients with VMT.¹⁹ SD-OCT may also discriminate between pseudocysts secondary to VMT and cystoid macular oedema.^{20,23}

SD-OCT has allowed a more accurate staging of IMH (Figure 9).³⁸ Visualisation of foveal anatomy (including intraretinal cavitation) can identify changes indicating impending macular holes, potentially allowing for early intervention.^{19,74} SD-OCT can also be used to accurately measure various characteristics of macular holes including base width, minimum linear diameter, height, and a variety of macular hole ratios including the macular hole index (Figure 12),^{75–78} as well as distinguishing between IMH, macular pseudohole, or lamellar macular hole.⁷⁹ An important clinical consideration is the choice of scanning protocol used especially when assessing macular holes—vertical and horizontal scans with a wide spacing between lines could miss areas of focal vitreous attachment or full-thickness retinal defects, or underestimate true IMH size. Using the lowest line spacing protocol available or a radial pattern scan through the fovea can reduce this risk.

In both VMT and IMH, SD-OCT permits accurate follow-up and monitoring of patients undergoing

surgical or other procedures, or over a period of observation.^{20,31,80} More accurate prognosis for vision recovery may be possible by assessing the structural integrity of the photoreceptors at the site of the IS/OS junction defect, the integrity of the external limiting membrane (ELM), and outer diameter of the foveal defect before and following intervention.^{46,79,80} Studies have also indicated that preoperative base diameter, inner opening diameter, and minimum linear diameter can predict the outcome of vitrectomy for IMH.⁸¹

Fluorescein angiography may be employed in some cases where it is suspected that other pathologies may be present, such as choroidal neovascularisation, parafoveal telangiectasia, or previous and clinically occult retinal vein occlusion.

Treatment options

Observation

In a small number of cases, VMT resolves spontaneously without intervention (reported incidences are 10–11%).^{82,83} The tenacity of the adhesion between the vitreous gel and macula determines the likelihood of spontaneous PVD.² One study utilising SD-OCT re-examined patients' VMT at a period of 4–12 months after the first assessment; persistent VMT was associated with the presence or development of ERM and also the largest horizontal VMA.⁸⁴ However, resolution is hard to predict, so observation is currently recommended as standard of care for at least 3 months before initiating any treatment in order to avoid unnecessary surgery.

In the Eye Disease Case–Control Study, after 3 years of follow-up in patients with pre-existing IMH, 21.7% demonstrated an enlargement; this rose to 37.1% after 6 years.⁵⁵ Spontaneous regression or resolution of IMH was observed in 9% of patients after 6 years of follow-up.⁵⁵ Over a period of at least 1 year, deterioration in VA of two Snellen lines or more has been reported for 30% of patients with stage 1, 68% with stage 2, 29% with stage 3, and 13% with stage 4 IMH.⁸⁵ However, central retinal detachment secondary to IMH appears to be limited to patients with high myopia.⁸⁶

Generally, most macular pseudoholes and lamellar macular holes tend not to progress anatomically over a period of several years and are usually not associated with significant decreases in VA.^{87,88} However, some macular pseudoholes may be associated with decreased VA in some cases (eg, with lamellar cleavage of the edges), and in such instances, surgery may be performed—vitrectomy with ERM and ILM peeling.⁸⁹ Maintenance of VA in eyes with lamellar macular holes is associated with preservation of the ELM.⁹⁰ As with macular pseudoholes, vitrectomy with ILM peeling may

be performed in patients with impaired VA or symptomatic distortion—optimal results are obtained when the IS/OS junction and ELM are intact.^{91,92}

Vitreotomy

Technology The primary aim of any intervention in patients with VMT and/or IMH is to release the residual VMA, facilitating a restoration of normal central retinal architecture, and with closure of a macular hole if present. Vitrectomy has been the only method available until now to achieve this.

Closed pars plana vitrectomy (PPV) (Figure 14) was first described by Machemer in 1971.⁹³ Subsequently, the

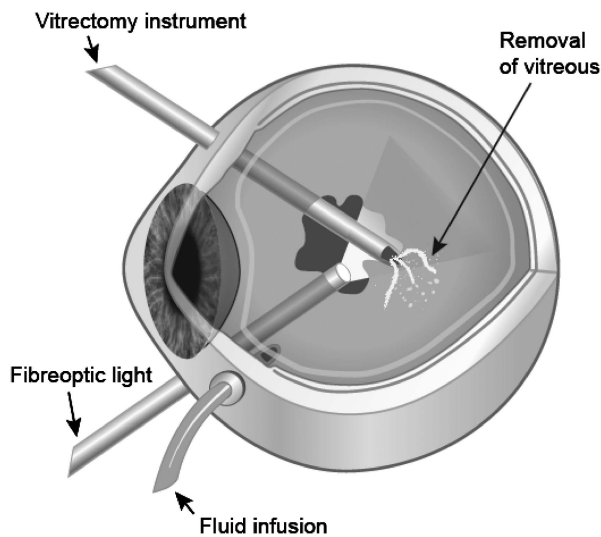


Figure 14 Pars plana vitrectomy.

technique has undergone several advancements with narrow-gauge transconjunctival sutureless vitrectomy (TSV) now being routinely carried out. 20-, 23-, 25-, and 27-gauge systems are all available and have relative advantages and disadvantages (Table 1). Enhancements in illumination and wide-field viewing systems have optimised the surgeon's view of the retina. In addition, cannulated and valved entry systems with high-speed efficient cutters have minimised retinal traction and trauma, reducing perioperative unintentional retinal break formation and postoperative retinal detachment.

Kelly and Wendel⁹⁴ first described vitrectomy to close macular holes in 1991 and since then a number of refinements and variations have been described. During vitrectomy, separation of the posterior hyaloid face from the retina is carried out by aspiration if not already present and the core and peripheral vitreous removed. Peeling of the ILM has been shown to increase MH closure rates. It is thought to work by: (1) removing residual adherent vitreous cortex remnants on the ILM surface; (2) removing associated fibrocellular collections; (3) removing the rigid and less compliant ILM (relative to the retina itself); and (4) causing a retinal glial cell proliferation that may paradoxically help macular hole contraction and repair.^{43,95} Peeling is generally carried out using a pinch-peel technique with fine-tipped forceps. Various aids to initiate peeling such as the Tano diamond dusted scraper are also used. The ILM is usually peeled to a radius of approximately one disc diameter around the hole.

A variety of dyes including indocyanine green (ICG), Trypan blue, and Brilliant Blue G can be used to aid visualisation of the ILM.^{71,72,96–98} They demonstrate varying degrees of ILM specificity and are sometimes

Table 1 Advantages and disadvantages of conventional sutured 20-gauge pars plana vitrectomy *vs* narrow-gauge transconjunctival systems with cannulated sclerotomies^{101,135,136,138,163–167}

	Advantages	Disadvantages
20-Gauge	<ul style="list-style-type: none"> More rigid instruments. Availability of angulated scissors. Greater potential illumination. Higher achievable flow rates. Less prone to clogging with dense material. 	<ul style="list-style-type: none"> Sutures needed to close conjunctiva and sclerotomies with postoperative surface discomfort and irritation. Higher rate of sclerostomy-related retinal breaks. Requirement for plugs to close sclerotomies when instruments removed from eye. Reduced globe stability with higher potential for surge.
Narrow-gauge	<ul style="list-style-type: none"> Less conjunctival disruption and faster surface recovery with less postoperative discomfort. Quick entry and exit from the eye. Less potential for entry site trauma and lower incidence of entry site-associated retinal breaks. Lower flow rates with narrower field flow effects and less retinal traction. Smaller cutter port size with more precise end cutting ability. Valved sclerotomies eliminate unwanted sclerostomy leakage. 	<ul style="list-style-type: none"> Postoperative hypotony with sclerostomy leak in some cases. Change in technique needed to use instruments Lower achievable flow rates. Occasional requirement to open conjunctiva and enlarge sclerostomy to introduce larger instruments. Lower infusion flow rates with higher resistance.

used sequentially to peel ERM if present and then ILM. Increasingly, agents designed to settle onto the retina in fluid are used to avoid the need for fluid-air exchange. Dyes are left on the retinal surface for the minimal time to allow staining (typically less than 1 min) before being washed out to reduce the possibility of toxic effects. In particular, there has been much debate about the risks of toxicity with ICG.

Following completion of vitrectomy and ILM peeling and careful checking of the peripheral retina for retinal tears, an air-fluid exchange is carried out, with subsequent gas exchange.^{97,98} Gas is used to facilitate hole closure by two key mechanisms. First, the surface (interfacial) tension of the gas across the hole prevents trans-hole fluid flow from the vitreous cavity and also reduces trans-retinal uveal-scleral outflow with reduced retinal oedema. The gas interface also acts as a surface to allow glial cell migration to bridge the gap between the retinal edges.^{43,99} A variety of gases have been used to achieve the above aims with a gradual change in practice from most surgeons using longer-acting gases such as perfluoropropane (C3F8) to an increasing use of shorter-acting gases such as sulphur hexafluoride (SF6) or even air.^{20,76,100,101} Silicone oil, both light and heavy, have been used by some surgeons following failure to close IMH at a first procedure.⁷⁷ Once the gas has been absorbed (or oil removed), the aqueous humour gradually fills the vitreous chamber. Vitrectomy with gas in the age group affected by IMH commonly results in cataract formation and phacoemulsification is commonly combined with vitrectomy to speed visual recovery.

Adopting a face-down posture after completion of PPV has been recommended conventionally, but it has been increasingly realised that this is not always necessary, particularly with smaller holes.^{77,102} Gas can still bridge the defect of a macular hole without face-down positioning as long as the patient does not lie supine for the whole duration.

With vitrectomy for VMT, again the main surgical aim is to remove the aberrantly attached posterior hyaloid face. ERM as described is a common accompaniment of VMT and ERM and/or ILM peeling is commonly carried out as well to remove all associated traction. Gas tamponade is not routinely used unless it is needed to address peripheral retinal pathology or to assist wound closure.

Clinical outcomes: VMT The majority of published studies reporting results of PPV specifically for VMT consist of small cohort studies. However, these all indicate a high success rate. In an early report regarding a series of 26 eyes, 15 demonstrated improvement in VA of at least 2 Snellen lines (75%), with 8 achieving 20/50 VA or better.¹⁰³ Similarly, in another series of 18 cases of patients undergoing PPV and ERM peeling, there was VA

improvement in 72% of the eyes, with six achieving 20/40 VA or better.¹⁰⁴ Among a different series of 29 eyes, following PPV VA was improved by ≥ 2 lines in 21.¹⁰⁵ Preoperative VA of 0.25 or better predicted a greater improvement in VA following surgery (0.42 vs 0.65 lines; $P = 0.006$). Similarly, in a larger series of 50 eyes, achievement of postoperative VA of 20/50 or better was demonstrated only in eyes with preoperative VA $\geq 20/100$ (66%).¹⁰⁶ In a retrospective review of 20 eyes with VMT that had undergone PPV with ERM peeling, mean VA improved from 20/122 before surgery, to 20/68 following the procedure ($P = 0.005$).¹⁰⁷

It is unclear if there is an additional benefit from ILM peeling in addition to removal of the VMT and ERM, but it is commonly practiced to ensure complete removal of surface traction. In a single study involving 30 eyes with VMT (VA $< 20/32$) undergoing PPV with ERM removal and ILM peeling, although retinal surface folds resolved within 1 month after the procedure, recovery of IS/OS retinal layer integrity was only achieved after 1 year. However, VA improved progressively during the 2-year follow-up period.¹⁰⁸

Improvement in VA following PPV for VMT is also correlated with the duration of symptoms, stage of VMT (stage 1, focal vitreofoveal hyaloidal attachment with perifoveal separation; stage 2, vitreomacular and papillomacular attachment; or stage 3, broad vitreofoveal attachment) and preoperative central macular thickness.¹⁰⁹ Mean VA improvement was significantly greater in patients with stage 1 VMT (2.82 ± 1.47 lines) vs stage 2 VMT (0.83 ± 1.17 lines) or stage 3 VMT (1.29 ± 0.49 lines) ($P = 0.036$ for trend).

Clinical outcomes: IMH Success rates in terms of closure for IMH with vitrectomy are generally high (reported 85–100%);^{77,100,110} success rates of TSV and conventional 20-gauge PPV appear equivalent.¹¹⁰ However, a number of IMH characteristics are thought to impact on successful closure following PPV. These include a smaller base diameter, smaller inner opening size, and shorter minimum linear dimension.^{77,81} Visual success is also correlated with base diameter, inner opening size, and minimum linear dimension. In a recent analysis from a multicentre database study in the UK, a total of 1078 eyes from 1045 patients underwent PPV for IMH (94% also had ILM peeling).¹¹¹ At 12 weeks after surgery, 119 of 476 evaluable eyes (48.6%) had achieved success (defined as ≥ 0.3 logMAR units improvement (equivalent to 2 Snellen lines)); this proportion increased to 58.3% at 52 weeks, while 8% had deteriorated by > 0.30 logMAR units.

A number of surgical aspects have been studied to assess their effect on success rates. Several randomised studies have been carried out on the efficacy of ILM peeling added to surgery. In the FILM study at 1 month

after the procedure, closure of the IMH was complete in 84% of the patients undergoing ILM peeling compared with 48% who did not undergo ILM peeling ($P < 0.001$).⁹⁷ However, there were no differences in IMH closure between the groups at 3 (92 vs 83%) and 6 months (94 vs 89%), reflecting the fact that patients with persistently open holes underwent repeat surgery. Indeed at 3–6 months after surgery, there was no significant difference between the groups for distance or near VA, or contrast sensitivity. A total of 31 patients (48%) who did not undergo ILM peeling required further surgery, of which 25 (38%) required ILM peeling during the follow-up period. Reopening of IMH was reported for one eye in the no ILM peeling group and none in the ILM peeling group. A recent Cochrane review also concluded that ILM peeling compared with no peeling increases the chance for an IMH to close with a single surgical procedure and reduces the chances of patients requiring additional surgery without unwanted side effects.¹¹² The authors added that as ILM peeling is likely to be cost-effective, it may be considered the best available option for individuals with IMH.

There is controversy, however, as to whether all sizes of macular holes require ILM peeling. In a study by Tadayoni *et al*,¹¹³ the authors proposed that ILM peeling offers no additional benefit to PPV with removal of any ERM when applied to eyes with IMH of $< 400 \mu\text{m}$ in diameter. Closure rates in these smaller holes were 100% for ILM peeling and 100% without ILM. In contrast, ILM peeling for IMH $\geq 400 \mu\text{m}$ resulted in successful closure in all holes, compared with 73.3% of holes without ILM peeling ($P = 0.015$). A retrospective study by the same group showed that retinal sensitivity was significantly reduced when comparing ILM peeling with no ILM peeling; microscotomas were also significantly more common in the ILM peeling group.¹¹⁴ In general, there are also some concerns about possible adverse effects of ILM peeling.¹¹⁵

There has been much debate regarding the effect of various dyes used to facilitate ILM peeling (especially ICG) and their effect on vision in particular. The results of individual studies have been inconsistent; however, a meta-analysis of pooled data from clinical trials has assessed the use of ICG in patients undergoing PPV and ILM peeling for IMH.⁹⁶ There was no difference in IMH closure rates between ICG and no stain or between ICG and other dyes. The rates of VA gain $\geq 20/40$ were comparable for eyes receiving ICG vs no dye at 1 year (odds ratio (OR): 0.82; 95% confidence interval (CI): 0.49–1.35; $P = 0.435$), but were lower for ICG vs other dyes (OR: 0.65; 95% CI: 0.43–0.97; $P = 0.033$). There was no difference for ICG vs no dye or ICG vs other dyes for rates of VA improvement ≥ 2 Snellen lines. There is some evidence of toxicity associated with dyes although again

results are difficult to interpret. In one study comparing triamcinolone with Infracyanine Green in patients undergoing PPV for IMH with ILM peeling, the latter was associated with deleterious effects on the photoreceptor cells.¹¹⁶

Numerous studies have reported the use of different types of tamponade following PPV for IMH. Initially, long-acting gases were always used but increasingly shorter-acting ones and air are used: and increasingly with gases the role of postoperative face-down posturing and its duration has been questioned. In a study of 156 eyes from 151 patients, PPV was performed with ILM peeling and either SF6 or air tamponade with postoperative face-down posturing.¹¹⁷ Equivalent hole closure rates were achieved ($> 90\%$ in both groups). A different study reported closure rates of 55% at 24 h and 76% at 48 h following surgery with room air tamponade and face-down positioning.¹¹⁸ In a separate cohort study, SF6 was compared with perfluoroethane (C2F6) in patients who did not assume a face-down posture after surgery.¹¹⁹ IMH closure was achieved in $> 85\%$ of patients in both groups. At 6 months after the procedure, mean VA improved from 0.78 logMAR to 0.38 logMAR in the SF6 group and from 0.81 logMAR to 0.44 logMAR in the C2F6 group. However, SF6 was absorbed more rapidly than C2F6, having completely disappeared at 2 weeks following surgery. In another study, SF6 was compared with C3F8 after PPV for IMH in 69 eyes.¹²⁰ IMH closure rate was 90% with SF6 and 91% with C3F8. At 6 months after surgery, mean VA significantly had improved in both groups (SF6, 0.32 logMAR, $P = 0.045$ vs baseline; C3F8, 0.52 logMAR, $P < 0.001$ vs baseline).

In patients with persistent IMH following initial PPV with ILM peeling and gas tamponade, the use of heavy silicone oil has been associated with high success rates for hole closure (92%).¹²¹ However, although when compared with C3F8 tamponade for primary IMH surgery, closure rates with silicone oil were comparable ($> 80\%$) in both groups, VA improvement to 20/70 or better was achieved in fewer patients receiving silicone oil than C3F8 (17.3 vs 73%).¹²² A separate study comparing these types of tamponade reported IMH closure rates of 65% for silicone oil and 91% with C3F8 ($P = 0.022$).¹²³ A higher percentage of patients in the silicone oil group also required a second procedure compared with the C3F8 group (35 vs 4%; $P = 0.006$). In addition, final median VA was superior for C3F8 (20/50) vs silicone oil (20/70; $P = 0.047$).

A recent Cochrane Review analyzed three randomised controlled trials directly comparing face-down posturing following macular hole surgery with no face-down posturing.¹²⁴ For macular holes $\leq 400 \mu\text{m}$, it was concluded that there was no significant effect of face-down posturing on successful hole closure.

However, two of the studies found that there was a significant benefit of face-down posturing on successful IMH closure when the diameter was $>400\ \mu\text{m}$. A more recent retrospective review of 208 eyes undergoing PPV with ILM peeling followed by C3F8 tamponade reported that in the absence of face-down positioning IMH closure was achieved in 81% of eyes, accompanied by an improvement in mean VA from 20/200 to 20/40.¹⁰² Another study obtained an IMH closure rate of 84% following vitrectomy with phacoemulsification (phacovitrectomy) and intraocular lens implantation followed by SF6 tamponade, without face-down positioning.⁷⁷

Combined phacovitrectomy has been compared with sequential vitrectomy and phacoemulsification (during the first year following vitrectomy) in 120 eyes with IMH and pre-existing cataract.¹²⁵ Best-corrected VA improved significantly at 6 months after phacovitrectomy, with no significant further improvement after this time. However, in the sequential procedure group, VA was only improved at the 1-year follow-up. IMH closure at 1 month after one surgical procedure was 100% in the phacovitrectomy and 96% in the sequential vitrectomy and phacoemulsification group. There is no clear evidence that combined phacovitrectomy affects the long-term results of PPV for IMH but visual recovery is quicker.

There is little literature regarding changes in quality of life following vitrectomy for IMH. However, in two studies involving a total of 101 patients, at 1 year following PPV statistically significant improvements in general vision, peripheral vision, close (near) and distance activities, social functioning, mental health and dependency were reported.^{66,126}

Safety and complications Vitrectomy can be incomplete, leaving remnants of vitreous cortex on the ILM, with the consequences of persisting traction and/or renewed proliferation of cells at the VRI, which may lead to later recurrent traction. ILM peeling can avoid this and indeed the rate of late reopening of macular holes is anecdotally higher without ILM peeling. However, mechanical manipulation of the VRI, including ILM peeling can cause iatrogenic damage to the macula including inadvertent impact site and tear formation although these are rare. Superficial retinal haemorrhages are not uncommon after ILM peeling although they do not seem to be visually significant in most cases.⁹⁷ As mentioned previously, ILM peeling can be associated with a number of other consequences, the effects of which are uncertain, including the appearance of a disassociated optic nerve fibre layer.^{127,128}

In case series and reviews of patients undergoing 20-gauge conventional PPV, the reported incidence of iatrogenic peripheral retinal breaks has been variable,

ranging from 6 to 36%.^{97,103,110,129–131} In eyes requiring surgical PVD induction (most cases of IMH and VMT), the risk of peripheral iatrogenic retinal breaks is approximately three times higher than in eyes with pre-existing complete PVD.^{131,132} The reported rates of peripheral retinal break formation appear to be lower with narrow-gauge TSV using cannulated sclerostomy systems with breaks reported in 11–16% of procedures, and only 3–6% related to sclerostomies.^{110,130,132–134} Retinal detachment has been reported in ~2–6% of patients undergoing PPV for IMH.^{97,129,132,133,136–139}

Symptomatic peripheral field defects are an uncommon finding ($<1\%$ of procedures) following PPV for IMH.^{140,141} These are usually temporal and possibly related to vitreous separation or the consequences of fluid/air-exchange during surgery.

Cataracts are very common following vitrectomy, especially in the >60 year-old age group and when long-acting gases are used. Progression of existing cataracts in patient undergoing PPV for IMH has been reported in 34% of patients at 12 months following the procedure.^{142,143} Combined phacovitrectomy has been widely adopted to avoid the need for subsequent cataract surgery. However, potential adverse effects of the procedure can be a higher incidence of posterior synechiae formation and intraocular lens-related complications and a small (~ 0.5 dioptre) myopic shift in refraction. Conversely, sequential surgery has been associated with a higher rate of posterior capsule rupture and other operative difficulties during the subsequent cataract surgery, associated with the lens-iris diaphragm syndrome after vitrectomy.^{144–146}

Minor vitreous haemorrhage (with spontaneous resolution) has been reported for $\sim 5\%$ of eyes undergoing 23-gauge TSV.¹³⁸ Hypotony related to wound leakage is a concern with sutureless PPV, occurring in a reported 3–16% of eyes.^{136,147} In the majority of cases, this resolves spontaneously and its incidence is reducing as sclerostomy entry systems improve. However, there is an increased risk of complications such as hypotony-related retinopathy, choroidal effusions, and choroidal haemorrhage in severe cases.^{101,147}

Endophthalmitis is very rare, occurring in ~ 0.02 – 0.05% of cases. Initially, narrow-gauge vitrectomy was thought to be associated with a higher incidence of endophthalmitis than 20-gauge PPV; however, this has not proven to be true.^{148,149}

Ocriplasmin

The principal aim of pharmacological vitreolysis is to cleave the VRI where a persistent VMA is present, resulting in complete PVD. First, plasmin, which acts by

breaking down the fibronectin and laminin within the VRI, was found to degrade the attachment of the collagen fibrils to the ILM following intravitreal injection in human cadaver eyes.^{150,151} Ocriplasmin, which is a recombinant truncated form of human plasmin, demonstrates a substantially longer half-life in the blood than plasmin but retains the biological actions of the intact enzyme.¹⁵²

The effects of ocriplasmin were firstly studied on human donor eyes.¹⁵² Intravitreal administration achieved a complete VRI separation at the two highest doses administered, leaving an almost bare ILM with few remaining collagen fibrils. In animal studies, intravitreal ocriplasmin demonstrated a dose-dependent degree of PVD induction.^{152–154} All PVDs occurred within 60 minutes of ocriplasmin administration, and histological assessments indicated that retinal integrity was maintained. In animals with complete PVD, the surface of the ILM was smooth and collagen fibrils were absent.

Ocriplasmin (Jetrea) has been licensed in Europe and the USA for treatment in patients with symptomatic VMA/VMT including when associated with MH less than 400 microns. Ocriplasmin has also recently been approved for funding by the UK's National Institute for Health and Care Excellence (NICE) in patients without ERM, but who have either VMT with severe symptoms or VMT with MH with or without severe symptoms.

Clinical efficacy

Ocriplasmin was initially evaluated before vitrectomy to assess its effectiveness in the achievement of complete PVD. A preliminary clinical study assessed intravitreal ocriplasmin at doses of 25, 50, 75 and 125 μg administered either 1–2 h, 24 h, or 7 days before planned PPV for VMT.¹⁵⁵ Increasing duration of exposure to ocriplasmin was associated with a progressive increase in the incidence of complete PVD achievement. In initial studies, a dose–response relationship for complete PVD was also observed. A subsequent Phase II, randomised, double-blind, placebo-controlled trial in 125 patients with VMT or IMH scheduled for PPV evaluated intravitreal ocriplasmin at doses of 25, 75, and 125 μg administered 7 days before surgery.¹⁵⁶ Complete PVD demonstrated at the time of vitrectomy was similar for placebo and ocriplasmin 25 μg (10 vs 14%), but dose-dependently higher with the 75 μg , and 125 μg doses (18 and 31%, respectively). Resolution of VRI abnormality precluding the need for vitrectomy was observed in 31% of patients randomised to ocriplasmin 125 μg at 35 days after administration, and in 28% of patients at 180 days. This dose of ocriplasmin was therefore selected for further evaluation. A separate Phase II study evaluated ocriplasmin in patients with VMA, with or without

IMH.¹⁵⁷ At 28 days after administration, resolution of VMA was achieved in 44% of patients receiving 125 μg ocriplasmin vs 8% of patients in the control group.

Two separate Phase III randomised, double-blind, placebo-controlled clinical trials with similar designs were conducted to assess the effects of a single intravitreal injection of ocriplasmin 125 μg in patients with VMT and/or IMH (holes <400 μm minimum linear diameter and with VMT to the edges of the hole).¹⁵⁸ At 7 days after treatment, the percentage of eyes with resolution of VMA was significantly greater with ocriplasmin than with placebo (OR: 5.20; 95% CI: 2.53–12.07; $P < 0.001$). After 28 days this superiority of ocriplasmin relative to placebo was maintained (26.5 vs 10.1%; OR: 3.28; 95% CI: 1.93–5.84; $P < 0.001$). Complete PVD was achieved in 13.4% of eyes receiving ocriplasmin and 3.7% of patients receiving placebo ($P < 0.001$). Closure of IMH was observed in 41% of eyes in the ocriplasmin group and 11% of eyes in the placebo group ($P < 0.001$). Smaller macular holes closed more frequently than larger ones, with a 58.3% closure rate in holes <250 μm and 24.6% closure in holes 250–400 μm in size. VA improved by at least three Snellen lines in a greater proportion of eyes in the ocriplasmin group relative to placebo. Resolution of VMA was significant for ocriplasmin vs placebo in both men (18.7 vs 5.5%; OR: 3.38; 95% CI: 1.25–15.75; $P = 0.01$) and women (30.3 vs 13.0%; OR: 2.94; 95% CI: 1.60–5.76; $P < 0.001$).¹⁵⁸ There was higher success rate of VMT release in patients with widths of VMA <1500 μm than those $\geq 1500 \mu\text{m}$, and a lower success rate in those with ERM than those without associated ERM (8.7 vs 37.4%). A subsequent multivariate analysis of data from these Phase III studies identified the following baseline characteristics as indicative of treatment success with ocriplasmin: the presence of a full-thickness IMH, VMA diameter $\leq 1500 \mu\text{m}$, phakic lens, absence of ERM, and patient age <65 years.¹⁵⁹

Quality of life was measured using the National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25).¹⁵⁸ Mean improvements from baseline to study endpoint were significant for ocriplasmin vs placebo for the items general vision ($P = 0.006$), distance vision ($P = 0.03$), dependency ($P = 0.009$), driving ($P = 0.03$), and the VFQ-25 composite score ($P = 0.007$).¹⁶⁰ In the placebo group, mean scores for general health, dependency, and driving all deteriorated from baseline to the end of the study.

Safety The safety profile of ocriplasmin has been evaluated in a number of clinical studies. The most commonly reported adverse events in the two Phase III trials included vitreous floaters (ocriplasmin, 16.8% vs placebo, 7.5%; $P = 0.002$), conjunctival haemorrhage (14.6 vs 12.8%), photopsia (11.8 vs 2.7%; $P < 0.001$), and injection-related eye pain (13.5 vs 5.9%; $P = 0.005$)

Table 2 Most frequently reported treatment-emergent ocular adverse events in two randomised, double-blind placebo-controlled studies comparing intravitreal ocriplasmin with placebo (adapted from Stalmans *et al*¹⁵⁸)

Adverse event	Placebo	Ocriplasmin	P-value ^a
	(n = 187) No. of events (%)	(n = 465) No. of events (%)	
<i>Any ocular adverse event</i>			
Vitreous floaters ^b	14 (7.5)	78 (16.8)	0.002
Photopsia ^b	5 (2.7)	55 (11.8)	<0.001
Conjunctival haemorrhage	24 (12.8)	68 (14.6)	0.53
Injection-related eye pain ^b	11 (5.9)	63 (13.5)	0.005
Blurred vision ^b	6 (3.2)	40 (8.6)	0.01
Visual impairment ^b	3 (1.6)	25 (5.4)	0.02
Increased intraocular pressure	10 (5.3)	18 (3.9)	0.50
Retinal tear	5 (2.7)	6 (1.3)	0.25
Cataract	17 (9.1)	26 (5.6)	0.13
<i>Any ocular serious adverse events^c</i>			
Macular hole	16 (8.6)	24 (5.2)	0.15
Retinal detachment	3 (1.6)	2 (0.4)	0.16
Reduced visual acuity	1 (0.5)	3 (0.6)	0.94

^a Calculated by the Cochran–Mantel–Haenszel test, stratified according to study.

^b Based on subjective reports by study participants.

^c Identified as such by the investigator and defined as one of the following: an event resulting in persistent or clinically significant disability, incapacity, or both; an event requiring in-patient hospitalisation or prolongation of an existing hospital stay; or an event that was considered to be medically important.

(Table 2).¹⁵⁸ Secondary macular hole development occurred in 5.2% of patients randomised to ocriplasmin and 8.6% of patients randomised to placebo. Retinal detachment was uncommon, reported for 0.4 and 1.6% of patients receiving ocriplasmin and placebo, respectively. Reduced VA occurred in less than 1% of patients in either treatment group, although clinical experience has shown that transient worsening of vision with increasing traction before vitreoretinal separation is achieved can occur and patients should be warned of this possibility.¹⁶¹

Animal studies have indicated an effect of ocriplasmin on fibronectin and laminin at the outer retina.¹⁶² However, to date only a single case has been reported, which was associated with transient vision loss.¹⁶¹ Importantly in patients receiving ocriplasmin, there have been no detrimental effects on the subsequent outcome of vitrectomy surgery.

Medical specialties and referral pathways

Patients will present to both medical and surgical retina specialists, as the symptoms of VMT and MH are not

specific to these disorders (eg, wet AMD is associated with similar symptoms). However, early referral of patients with VMT and MH will allow assessment and optimal management. In particular, patients with MH are best seen when VMT is present and the hole is small, as the results of intervention are favourable. Such cases with an MLD of less than 400 microns are amenable to treatment with ocriplasmin. A fast-track referral system such as that in place for patients with wet AMD should be available. However, ocriplasmin is not effective in all cases treated. Importantly the effect of ocriplasmin on vitreous separation is seen within the first month.

Therefore, in order to avoid surgical delay, patients could be listed for vitrectomy (certainly for IMH) at the same time as ocriplasmin is administered. This means that if results with ocriplasmin are not optimal waiting time is not further prolonged.

Current guidelines

There are currently no published consensus guidelines for the management of VMT. However, some general recommendations can be made. Patients should be observed for 2–3 months to see if spontaneous resolution occurs, although this is dependent on symptom severity and impact on the individual patient’s quality of life. If there is no resolution, treatment with ocriplasmin should be considered, taking into account factors such as the width of the VMA, presence of ERM, the status of the affected eye’s lens, and patient age.^{158,159} Surgery, as opposed to ocriplasmin is recommended if significant ERM is present.

IMH should be treated early, especially if symptoms are significant and affecting quality of life. Ocriplasmin can be considered if hole diameter is <400 μm and VMT is also present. Patient-dependent factors such as systemic morbidity and ability to undergo surgery must also be taken into account. However, if the IMH is not successfully closed after a maximum of 1 month after ocriplasmin administration, vitrectomy should be performed. If an IMH is >400 μm diameter and VMT is absent, vitrectomy is routinely recommended as the primary procedure in all cases. Under these circumstances, ILM peeling and probably face-down posturing improves results. Simultaneous cataract surgery can be performed, especially if the patient is aged more than 60 years. The minimum effective amount of dye should be used for staining.

Future research

A number of unanswered questions remain regarding the pathophysiology of, and current interventions for, VMT and IMH. A greater understanding of the role of

VMT in the pathophysiology of wet AMD and DMO could help to advance treatments of these disorders. In addition, further and more precise determination of the IMH features that are associated with the requirement for face-down posturing and/or ILM peeling for successful PPV is needed. The role of surgery in symptomatic LMH also needs clarifying.

Defining patient groups in which response rates to ocriplasmin are most favourable is a key priority as well as optimising the timing of intervention in the course of disease. The potential benefits of ocriplasmin in inducing vitreous separation with a clean ILM surface and the possible benefit of vitreous separation early in the disease course of number of conditions including diabetic retinopathy could also be investigated.

Summary

PVD is a common phenomenon in the aging eye. However, this may be complicated by VMT (with or without ERM) and/or IMH. Technologies such as OCT allow more accurate visualisation and measurement of the macular anatomy, facilitating treatment decision-making. PPV remains the primary treatment option for many patients with VMT or IMH. However, ocriplasmin may allow induction of PVD in a non-invasive manner in some cases. Further research is needed with respect to greater understanding of the pathophysiology underlying the development of VMT/IMH, together with the relationships between these disorders, AMD and DMO.

Conflict of interest

DHW Steel has been the recipient of honoraria and fees for presentations at meetings and congresses and for participating in Advisory Boards from Alcon and ThromboGenics. He has also received unrestricted grant support from Novartis. AJ Lotery has been the recipient of honoraria and fees for presentations at meetings and congresses and for participating in Advisory Boards from Novartis.

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Appendix

Appendix Ocriplasmin PI—UK and Ireland

JETREA[®] ▼ 0.5 mg/0.2 ml concentrate for solution for injection (ocriplasmin) Prescribing Information

(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Type I glass vial containing 0.2 ml concentrate for solution for injection. After dilution with 0.2 ml sodium chloride 0.9% solution for injection, 0.1 ml of the diluted solution contains 0.125 mg ocriplasmin. **Indication(s):** Treatment of vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter less than or equal to 400 microns. **Posology and method of administration:** *Adults, including the elderly:* Intravitreal injection of 0.125 mg (0.1 ml of the diluted solution) to the affected eye once only as a single dose. *Children and adolescents:* Not recommended. **Hepatic and renal impairment:** No dosage adjustment necessary. **Contra-indications:** Hypersensitivity to ocriplasmin or any of the excipients. Active or suspected ocular or periocular infections. **Warnings and precautions:** Proper aseptic injection techniques must always be used and patients should be monitored for any side effects such as intraocular inflammation/infection and elevation in IOP. Patients should be instructed to report symptoms of intraocular inflammation/infection or any other visual/ocular symptoms without delay. Concurrent administration to both eyes or repeated administration in the same eye is not recommended. Clinical data is not available on concomitant use with

VEGF-inhibitors. Treatment is not recommended in patients with large diameter macular holes, high myopia, aphakia, history of rhegmatogenous retinal detachment, lens zonule instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration (AMD) and vitreous haemorrhage. There is potential for lens subluxation or phacodonesis. Exercise caution if treating patients with non-proliferative diabetic retinopathy, history of uveitis or significant eye trauma. Ocriplasmin efficacy is reduced in patients with an epiretinal membrane or a diameter of VMA > 1500 microns. Due to potential increase in tractional forces, there is a risk of occurrence of new or enlarged macular holes. There is a risk of significant but transient loss of visual acuity during the first week after the injection. **Interactions:** Formal studies have not been performed. Systemic interactions are not anticipated. Administration in close temporal association, in the same eye as other medicinal products may affect the activity of both products and is not recommended. **Pregnancy and lactation:** Do not use unless clearly necessary. *Fertility:* No fertility data are available. **Effects on ability to drive and use machines:** If visual disturbances occur, wait until vision clears before driving or operating machinery. **Undesirable effects:** *Very common:* vitreous floaters, eye pain, conjunctival haemorrhage. *Common:* visual acuity reduced, visual impairment, vision blurred, intraocular pressure increased, metamorphopsia, conjunctival oedema,

eyelid oedema, photopsia, conjunctival hyperaemia, ocular hyperaemia, retinogram abnormal, eye irritation, dry eye, foreign body sensation in eyes, eye pruritus, ocular discomfort, photophobia, chromatopsia. Serious: retinal haemorrhage, vitreous haemorrhage, retinal tear, retinal detachment, macular hole, macular degeneration, retinal degeneration, macular oedema, retinal oedema, retinal pigment epitheliopathy, vitreous adhesions, vitritis, anterior chamber cell, anterior chamber flare, iritis, vitreous detachment, transient blindness, lens subluxation, scotoma, visual field defect, hyphaema, pupils unequal, corneal abrasion, anterior chamber inflammation. *In addition:* diplopia, miosis, eye inflammation, conjunctival irritation. Prescribers should consult the SmPC in relation to the side effects. **Overdose:** Clinical data are limited. If an overdose occurs, close monitoring is recommended.

Incompatibilities: Must not be mixed with other medicinal products except for the specified diluent. **Special Precautions for Storage:** Store frozen at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** 1 \times 0.2 ml vial £2,500. **Ireland Price:** €3,099. **MA Number(s):** EU/1/13/819/001. **Further information available from the MA holder:** ThromboGenics NV, Gaston Geenslaan 1, B-3001 Leuven, Belgium. **Distributor:** Alcon Laboratories (UK) Limited, Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR. **Date of preparation:** June 2013 (V2).

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Alcon Medical Information. Tel: 0871 376 1402. Email: gb.adr@alcon.com