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REVIEW

- 1363 Conundrum of vitamin D on glucose and fuel homeostasis
Chang Villacreses MM, Karnchanasorn R, Panjawatanan P, Ou HY, Chiu KC
- 1386 Review of the management of sight-threatening diabetic retinopathy during pregnancy
Choo PP, Md Din N, Azmi N, Bastion MLC
- 1401 Epidemiology of type 2 diabetes in the Middle East and North Africa: Challenges and call for action
El-Kebbi IM, Bidikian NH, Hneiny L, Nasrallah MP
- 1426 Dipeptidyl peptidase-4 inhibitor-induced autoimmune diseases: Current evidence
Roy A, Sahoo J, Narayanan N, Merugu C, Kamalanathan S, Naik D
- 1442 Cellular targets in diabetic retinopathy therapy
Rodríguez ML, Millán I, Ortega ÁL
- 1463 Holistic perspective of the role of gut microbes in diabetes mellitus and its management
Alagiakrishnan K, Halverson T
- 1479 Non-alcoholic fatty liver disease in diabetes: When to refer to the hepatologist?
Khandelwal R, Dassanayake AS, Conjeevaram HS, Singh SP

MINIREVIEWS

- 1494 Improving nutrition for the prevention of gestational diabetes: Current status and perspectives
Popova PV, Pustozarov EA, Tkachuk AS, Grineva EN
- 1507 Salivary resistin level and its association with insulin resistance in obese individuals
Abdalla MMI
- 1518 Psychosocial factors affecting the etiology and management of type 1 diabetes mellitus: A narrative review
Turin A, Drobnič Radobuljac M
- 1530 Sugar intake from sweetened beverages and diabetes: A narrative review
Tseng TS, Lin WT, Gonzalez GV, Kao YH, Chen LS, Lin HY
- 1539 Role of an acidic environment in the treatment of diabetic foot infections: A review
Nagoba B, Gavkare A, Rayate A, Mumbre S, Rao A, Warad B, Nanaware N, Jamadar N
- 1550 Diabetes and COVID-19: Role of insulin resistance as a risk factor for COVID-19 severity
Gangadharan C, Ahluwalia R, Sigamani A

- 1563** Obesity and bariatric surgery in kidney transplantation: A clinical review

Veroux M, Mattone E, Cavallo M, Gioco R, Corona D, Volpicelli A, Veroux P

META-ANALYSIS

- 1576** Effectiveness of drug interventions in nonalcoholic fatty liver disease: A network meta-analysis

Huang YZ, Yang GY, Wang C, Chen XY, Zhang LL

ABOUT COVER

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Review of the management of sight-threatening diabetic retinopathy during pregnancy

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Abstract

Diabetes mellitus (DM) is a noncommunicable disease reaching epidemic proportions around the world. It affects younger individuals, including women of childbearing age. Diabetes can cause diabetic retinopathy (DR), which is potentially sight threatening when severe nonproliferative DR (NPDR), proliferative DR (PDR), or sight-threatening diabetic macular oedema (STDM) develops. Pregnancy is an independent risk factor for the progression of DR. Baseline DR at the onset of pregnancy is an important indicator of progression, with up to 10% of women with baseline NPDR progressing to PDR. Progression to sight-threatening DR (STDR) during pregnancy causes distress to the patient and often necessitates ocular treatment, which may have a systemic effect. Management includes prepregnancy counselling and, when possible, conventional treatment prior to pregnancy. During pregnancy, closer follow-up is required for those with a long duration of DM, poor baseline control of blood sugar and blood pressure, and worse DR, as these are risk factors for progression to STDR. Conventional treatment with anti-vascular endothelial growth factor agents for STDM can potentially lead to foetal loss. Treatment with laser photocoagulation may be preferred, and surgery under general anaesthesia should be avoided. This review provides a management plan for STDR from the perspective of practising ophthalmologists. A review of strategies for maintaining the eyesight of diabetic women with STDR with emphasis on prepregnancy counselling and planning, monitoring and safe treatment during pregnancy, and management of complications is presented.

Key Words: Sight-threatening diabetic retinopathy; Severe nonproliferative diabetic retinopathy; Proliferative diabetic retinopathy; Diabetic macula oedema; Pregnancy;

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Panretinal photocoagulation

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Core Tip: Progression of diabetic retinopathy (DR) to the sight-threatening DR (STDR) is rare during pregnancy but can cause significant ocular morbidity and distress to the mother. Good prepregnancy and intrapartum control of systemic risk factors, especially blood sugar and blood pressure, and adequate prepregnancy treatment of STDR will reduce complications during pregnancy. When STDR develops, conventional therapy for nonpregnant individuals may not be applied. This includes avoidance of anti-vascular endothelial growth factor agents conventionally for diabetic macular oedema and proliferative DR (PDR), especially during early trimesters. Panretinal photocoagulation is a safe option for PDR. Surgical treatments should be performed under local anaesthesia or preferentially deferred until postpartum.

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INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disease that involves multiple organs and may cause severe visual impairment. DM is known to affect several ocular structures, including the extraocular muscles, the intraocular lens, the optic nerve, and the retina. However, diabetic retinopathy (DR) is the most common and leading cause of blindness among working-age adults in developing countries[1]. Of 285 million people worldwide with diabetes in 2010[2], approximately one-third have signs of DR, and one-third of these patients may have vision-threatening retinopathy, defined as severe nonproliferative DR (NPDR), proliferative DR (PDR), or diabetic macular oedema (DME)[3]. In Southeast Asia alone, the total number of people with diabetes is expected to reach more than 140 million by 2040. Over 20 years, the prevalence has more than doubled among Malaysians aged 30 or more years, with a prevalence of 22.6% in 2013[4,5].

CLINICAL FEATURES OF DR

DR can be classified into several stages: (1) Mild NPDR characterized by increased vascular permeability; (2) Moderate NPDR depicted by vascular closure with less than 20 microaneurysms; (3) Severe NPDR, which is identified as any of the following clinical features: Microaneurysms in all 4 quadrants, venous beading in 2 or more quadrants, and intraretinal microvascular abnormalities in 1 or more quadrant; (4) Very severe NPDR if they have 2 or more of the criteria for severe NPDR; and (5) PDR which is characterized by the growth of new blood vessels (neovascularization) on the optic disc, retina, or on the posterior surface of the vitreous. DME is characterized by retinal thickening from leaky blood vessels that can develop at any stage of DR.

The progression of DR during pregnancy increases the frequency of perinatal follow-ups and may necessitate stressful treatments[6]. Sight-threatening DR (STDR) can cause ocular morbidity, which can lead to psychological distress in new mothers [7]. Poor vision may also lead to adverse effects on newborns through neglect and postnatal depression in the mother[7].

RISK FACTORS FOR DR PROGRESSION

The incidence of DR is highly dependent on the duration and control of diabetes, and risk factors such as hyperglycaemia[8,9], hypertension[10], dyslipidaemia[11], and

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nephropathy[12] may accelerate DR progression in both pregnant and nonpregnant individuals.

In women with pre-existing DM, pregnancy is also known to be associated with worsening DR[13]. As the prevalence of type 1 DM (T1DM)[14] and type 2 DM (T2DM)[15] increases globally, recent studies have found that the incidence of DR in early pregnancy is approximately 63% in T1DM[16] and 14% in T2DM[13]. The adverse effects of pregnancy on retinal status occur by the end of the second trimester and regress after delivery, but some severe cases may persist into the first year postpartum[13,17-19]. Risk factors such as poor glycaemic control during pregnancy [13], longer duration of diabetes before conception[20], rapid normalization of glycated haemoglobin (HbA1c) at the beginning of pregnancy[20], hypertension[21], and preeclampsia[22] may influence the development and progression of DR during pregnancy.

The severity of DR at conception also has an impact on DR progression during pregnancy, as progression was more significant in pregnant women with moderate and severe forms of DR than in those with mild or no DR[16]. According to the Diabetes in Early Pregnancy Study, approximately 55% of pregnant women with moderate-to-severe NPDR and 21% with mild NPDR showed deterioration of DR[20]. A review by Morrison *et al*[23] found that when NPDR was present at baseline, 30.2% worsened, and 9.8% progressed to proliferative disease[23]. Macular oedema typically occurs alongside proteinuria or hypertension and may progress throughout pregnancy and resolve during the postpartum period; however, some cases may persist and cause long-term vision loss[24].

PREPARING FOR DR PROGRESSION IN PREGNANT DIABETICS

Screening and pre-pregnancy counselling and treatment

Screening for DR is an important aspect of diabetes management, as it aims to detect DR as early as possible to enable timely treatment and prevent vision loss[25]. Diabetic women should have a preconception retinal screening and counselling on the risk of development and progression of DR, as well as comprehensive care by a multidisciplinary team consisting of an endocrinologist, an ophthalmologist, and a perinatologist [26]. Comprehensive eye assessment, tight glycaemic control, and other assessments will be performed throughout the pregnancy period[27]. The duration of the follow-up is dependent on the stage of DR; the more severe the DR is at diagnosis during the initial check-up, the more frequent the follow-up schedule will be. Maximal control of both glucose levels and blood pressure is essential in the treatment of DR during pregnancy[16].

Laser photocoagulation for DR

Currently, scatter or panretinal photocoagulation (PRP) is a preferred treatment modality for all patients, including pregnant women with DR, which involves applying laser burns on the retina while sparing the central macular area to reduce the ischaemic drive and the risk of vision loss[28]. In an unfortunate event of DR progression, pregnant women with severe NPDR and PDR at the preproliferative stage may consider either scatter or PRP, as both are effective and safe treatments with minimal side effects to the foetus[29,30]. Although the results from protocol S of DRCR.net found that both anti-vascular endothelial growth factor agents (anti-VEGF) and PRP are effective for PDR, anti-VEGF in pregnancy should be avoided whenever possible to minimize the placental transfer of drugs and risk to the foetus[30,31]. However, PRP treatment is associated with potential side effects, including worsening of macular oedema that may lead to transient or permanent vision loss, peripheral visual field defects, night vision loss, loss of contrast sensitivity, potential complications from misdirected or excessive burns, and progression of visual loss[32].

Anti-VEGF agents for PDR and DME in pregnancy

VEGF, an endothelial-cell-specific angiogenic factor[33], was suggested to be the primary mediator of diabetic retinal neovascularization, as its concentration in ocular fluid samples from patients with PDR was found to be significantly increased compared to samples from patients with NPDR[34]. Since then, clinical studies have suggested that anti-VEGF therapy is effective for PDR[30], and various anti-VEGF drugs, such as pegaptanib, ranibizumab, bevacizumab, and aflibercept, have been used. Pegaptanib (Macugen®; Pfizer Inc.) is a 28-base ribonucleic acid aptamer that specifically binds to and blocks the activity of the 165 amino acid isoform of VEGF

(VEGF₁₆₅)[35] and was approved by the United States Federal Drug Administration (FDA) for the treatment of neovascular age-related macular degeneration in 2004[36]; administration of a 0.3 mg (0.9 mL) dose is recommended once every six weeks by intravitreal injection. The use of pegaptanib has been shown to reduce retinal thickness and improve vision in PDR[37] and macular oedema[38]. However, its use worldwide and in Malaysia for DME and PDR in nonpregnancy diabetic patients has been largely superseded by the other 3 anti-VEGF agents.

Ranibizumab (Lucentis®; Genentech Inc.) is a humanized monoclonal antibody fragment directed at all isoforms of VEGF-A and contains only the Fab fragment of the parental anti-VEGF antibody with a weight of 48 kDa[39]. The DR Clinical Research Network's (DRCR.net) Protocol S study found that eyes treated with ranibizumab were less likely to have vitreous haemorrhage (VH) and progress from severe NPDR to PDR than those treated with PRP[30]. The use of ranibizumab 0.3 to 0.5 mg (0.05 mL) as a monthly intravitreal injection attained FDA approval for the treatment of all forms of DR in 2017.

Bevacizumab (Avastin®; Genentech Inc.), a full-length recombinant humanized monoclonal immunoglobulin G1k antibody weighing 149 kDa, which inactivates all VEGF isoforms[39], was FDA-approved as a treatment for colorectal carcinoma in 2004. It is used as an off-label therapy by many ophthalmologists, as trials found its side-effect profile with doses of either 1.25 mg or 2.5 mg (0.05 mL) to be similar to ranibizumab[40]. A 2-year randomized controlled trial also provided evidence supporting the use of bevacizumab for persistent centre-involving macular oedema [41].

Aflibercept (Eylea®; Regeneron Inc.) is a 115 kDa recombinant fusion protein that consists of VEGF-binding domains for human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1 and binds to all isomers of the VEGF-A family [38]. In 2014, the FDA approved aflibercept for the treatment of macular oedema after significant improvements in the primary endpoint of mean change in best-corrected visual acuity were achieved for the aflibercept-treated group in completed phase III VIVID and VISTA[42] trials, and the 52-wk visual and anatomic superiority of the intravitreal aflibercept injection group was sustained through week 100[43]. The Panorama trial[44] was then conducted to investigate aflibercept for the improvement of moderate-severe to severe NPDR without macular oedema, and the safety data were consistent with the results of phase III VIVID and VISTA trials, and the outcome was sustained through week 100[45]; thus, it obtained FDA approval for the treatment of DR in 2019. The recommended dosage of aflibercept injection for the treatment of macular oedema and DR is 2 mg (0.05 mL) every 8 wk after five initial monthly injections.

VEGF also plays a role in the maintenance of foetal and placental vasculature[46]; thus, a reduction in VEGF expression has been linked with defective embryogenesis and foetal loss in humans[47]. Studies also found that the inhibition of VEGF activity and signalling pathways may lead to hypertension[48-50]. Despite this, the relationship between VEGF, hypertension, and preeclampsia is poorly understood. The teratogenicity of anti-VEGF drugs have been explored, categorized, and detailed by the FDA as follows[31]: Pegaptanib has been assigned to Pregnancy Category B, where no teratogenicity was found in mice when given an intravenous dose of up to 40 mg/kg/d (approximately 7000 times the recommended human dose of 0.3 mg per eye), while human studies are not yet available[51]; ranibizumab is designated Pregnancy Category C, where an embryo-foetal developmental toxicity study was performed on pregnant cynomolgus monkeys, and skeletal abnormalities were found in foetuses from monkeys treated with a dose of 1 mg/eye (approximately 13 times higher than predicted mean-steady stage C_{max} levels with single eye treatment in humans); no skeletal abnormalities were observed at the lower dose of 0.125 mg/eye (equivalent to C_{max} levels with single eye treatment in humans), and no adequate and well-controlled studies of the administration have been conducted in pregnant women [52]; bevacizumab has been assigned to Pregnancy Category C, as pregnant rabbits dosed with 10 mg/kg to 100 mg/kg (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during day 6-18 of gestation showed decrease in maternal and foetal body weights, increased number of foetal resorptions, skeletal deformities, and corneal opacity in all doses, while controlled data are not yet available in human pregnancy[53]; and aflibercept is designated Pregnancy Category C, where embryo-foetal development studies on rabbits with intravenous doses of ≥ 3 mg/kg have revealed evidence of embryo-foetal toxicity such as post-implantation loss and foetal malformations including skeletal abnormalities in all doses, while no controlled data are yet available in pregnant women[54].

The pharmacokinetics of these anti-VEGF drugs have been tested in animals and humans, but not all pharmacokinetic values in humans have been obtained. Nevertheless, the pharmacokinetic characteristics of these 4 drugs appear to be similar. Following intravitreal injections, these anti-VEGF drugs leave the eye by crossing the retina and retinal pigment epithelium to the choroidal circulation, passing through the ciliary body and iris, or moving into the anterior chamber by diffusion and bulk flow before exiting through the trabecular meshwork, and none of the drugs degrades within the eye[55]. Systemic half-lives vary from hours to weeks before drug elimination *via* glomerular filtration or pinocytotic elimination occurs.

Pegaptanib was found to have an intravitreal half-life of 3.9 d in monkeys[56] and an estimated half-life of 7 d in humans. After entering the systemic circulation in humans, the maximum serum concentration is reached in 1–4 d, and the serum half-life is 10 d. It is metabolized by endonucleases and exonucleases, which are then excreted primarily in the urine. On the other hand, after intravitreal injection into rabbits, ranibizumab has a half-life of 2.6–2.88 d[57–59] with a maximum aqueous concentration after 3 d. Ranibizumab fully penetrates the retina one day after injection, and the concentrations in the serum are either very low (1/10000 that of the vitreous) [58] or undetectable[59]. The half-life of ranibizumab in monkeys is 3 d, and serum concentrations are 1000-fold lower than those in the vitreous[60]. Intravitreal ranibizumab is found to distribute rapidly to the monkeys' retina within 6–24 h[60]. The half-life of intravitreal ranibizumab in humans is estimated to be 4.8–9 d, with serum concentrations approximately 90000-fold lower than intraocular concentrations [55]. The intravitreal and serum half-lives of bevacizumab in rabbits are 4.32 and 6.8 d, respectively[61,62], with a maximum serum concentration reached in 8 d. After intravitreal injections in rabbits, bevacizumab appeared in the subretinal space within 2 h [63], the inner retina and choroid within the first day, and the outer layers and choroid in subsequent days, but no drugs were found at 4 wk[64]. The half-life of intravitreal bevacizumab in a human was estimated to be 6.7–10 d depending on the use of either a one-compartment model or two-compartment model[65–68], while the half-life of bevacizumab in human serum is 17–21 d, similar to that of other full-length antibodies. Intravitreal aflibercept has a half-life of 4.7 d in rabbits[69] and an estimated 9 d in humans based on the intermediate size of the molecule (between ranibizumab and bevacizumab), while bound aflibercept in human serum has a half-life of 18 d[70]. Table 1 summarizes the structural and pharmacokinetic characteristics of the four anti-VEGF drugs. No study has been found to determine whether these drugs cross the placenta in pregnant women.

Several studies on the use of ranibizumab and bevacizumab in pregnant women have been reported of which some have been summarized by Polizzi and Mahajan [31]. Most of the studies in pregnant women are case reports, and initial intravitreal ranibizumab was given either 8–17 wk post last menstrual period (LMP)[70] or in the third trimester[71,72]; all reported no complications.

However, intravitreal anti-VEGF injections given as early as 5 wk postconception were associated with miscarriage within a week[73]. A total of 8 papers comprising 16 pregnancies in 15 women using intravitreal bevacizumab have been published since 2009[74–83]. The injection was given between a few days before or after the LMP and during the third trimester. There were 5 cases of abortion[76,79,82,83] and one case of pre-eclampsia[80] after the use of intravitreal bevacizumab. Petrou *et al*[76] described 2 women who received intravitreal bevacizumab at approximately 4 and 3 wk of gestation, respectively, followed by spontaneous miscarriage 7 and 10 d, respectively, after administration of the drug[76]. Gómez Ledesma *et al*[79] also reported a 41-year-old woman who received intravitreal bevacizumab a few days before or after the LMP and suffered a miscarriage approximately 7 wk after the injection[79]. Kianersi *et al*[82, 83] reported pregnancy loss within 18 to 24 h in two patients who received intravitreal bevacizumab injection while they were between 10 and 12 wk pregnant[82,83]. Intravitreal bevacizumab given preconception and continued after 29 wk of gestation was associated with preeclampsia requiring urgent caesarean section[80].

Despite these reports of spontaneous miscarriages and preeclampsia occurring after intravitreal anti-VEGF injections given within 13 wk of gestation, other reports did not find adverse events with injections given within the same time frame[70,74,75,77,78,80, 81]; thus, it is uncertain whether anti-VEGF therapy played a role in these pregnancy losses, as the rate of spontaneous miscarriage is between 15% and 20%[84] and may increase to as high as 41% if maternal age is over 35 years[85]. There were no reports on pegaptanib and aflibercept being administered in pregnant women. Hence, the use of anti-VEGF should be weighed against the possible risk of foetal developmental abnormalities or pregnancy loss and should only be administered following a thorough discussion with the patient and consultation with an obstetrician, and the

Table 1 Structural and pharmacokinetic characteristics of the four anti-vascular endothelial growth factor drugs[55]

	Pegaptanib	Ranibizumab	Bevacizumab	Aflibercept
Structure	Pegylated aptamer	Recombinant monoclonal antibody fragment (Fab)	Recombinant monoclonal antibody (Mab)	Fusion protein
Molecular weight (kDa)	50	48	149	115
Recommended dose (volume)	0.3 mg (0.9 mL)	0.5 mg (0.05 mL)	1.25 mg (0.05 mL)	2 mg (0.05 mL)
Intravitreal half-life (d)	3.9 (monkeys)	2.6-2.88 (rabbits) 3-3.2 (monkeys) 7.1 (humans)	4.32-6.61 (rabbits) 3.1 (monkeys) 6.7-10 (humans)	4.5-4.7 (rabbits)
Serum half-life humans (d)	10	0.25	21	18

potential benefit outweighs the potential risk to the foetus. Indeed, DM patients of child-bearing age should have PDR and DME treated before conceiving. This even means the need for contraception during anti-VEGF treatment.

Topical nonsteroidal anti-inflammatory agents in pregnancy

Apart from VEGF, elevated inflammatory markers have been found in patients with DR, which suggests that inflammation may play a role in the pathogenesis of DR[86] and macular oedema[87,88]. Both animal and human studies have found increased levels of inflammatory mediators and prostaglandins (PGs) in DR in the vitreous cavity[89-91], and prostaglandin E₂ levels correlate with vitreous levels of VEGF[92]. As topical nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of cyclooxygenase enzymes and reduce the synthesis of proinflammatory PGs with few documented risks, they have recently become readily available in the form of topical ophthalmic formulations[93]. New topical NSAIDs such as nepafenac (Nevanac®; Alcon Inc.) were formulated to be able to reach the posterior segment of the eye[94, 95]. It rapidly penetrates the cornea and is deaminated by intraocular hydrolases in uveal tissue and retina to form the active metabolite amfenac[96].

Several small randomized case studies on the use of topical nepafenac 0.1% for the treatment of DME have been published[97-100] and revealed the effectiveness of the drug and improvement in visual acuity and retinal/foveal/macular thickness. However, a phase II, multicentre, double-masked randomized clinical trial conducted by DRCR.net found that topical nepafenac 0.1% three times a day for a year on eyes with noncentral DME does not show a beneficial effect on OCT-measured retinal thickness or visual acuity outcomes[101], which is in contrast to the results of other smaller, randomized published case reports. Small quantifiable plasma concentrations of nepafenac and amfenac have been found in subjects 2-3 h after topical administration, and the C_{max} of nepafenac and amfenac in serum was approximately 0.31 and 0.42 ng/mL, respectively[102]. The elimination of orally administered nepafenac in rats was shown to be in the urine (57%) and faeces (40%) over 7 d[103]. The FDA has also categorized nepafenac under pregnancy category C, as reproduction studies performed in rabbits and rats at oral doses of up to 10 mg/kg/d have revealed maternal toxicity and no teratogenicity[104]. Animal exposure to nepafenac and amfenac was approximately 260- to 2400-fold human plasma exposure at the recommended human topical ophthalmic dose for rats and approximately 80- and 680-fold human plasma exposure for rabbits, respectively, at this dose. Dystocia increased post-implantation loss, reduced foetal weight and growth, and reduced foetal survival in maternal rats when given doses of ≥ 10 mg/kg. Although nepafenac could cross the placental barrier in rats, no adequate and well-controlled studies in pregnant women have been conducted; therefore, nepafenac should be used in pregnancy only if the potential benefit outweighs the potential risk to the foetus and should be avoided in the third trimester due to the known effects of prostaglandin biosynthesis inhibition on the foetal cardiovascular system (closure of ductus arteriosus)[105].

Vitrectomy for complications of STDR in pregnancy

VH secondary to PDR is one of the most common vision-threatening complications of DR other than DME. In mild to moderate cases of VH, PRP is performed when possible to prevent further episodes of VH, and it may eventually resolve spontaneously[106]. However, approximately 5% of PDR cases develop VH even after PRP is

initiated, which often requires pars plana vitrectomy (PPV)[107], a technique introduced in the 1970s[108]. Despite vision improvement reported in approximately 75% of PDR patients after PPV, major complications associated with PPV include cataract formation, elevated intraocular pressure, recurrent vitreous cavity haemorrhage (early, delayed, or persistent), iatrogenic retinal breaks, tractional and rhegmatogenous retinal detachment, and neovascular glaucoma[109]. Several studies have been conducted on the use of anti-VEGF drugs as a treatment for VH due to PDR and found that intravitreal ranibizumab[110], bevacizumab[111,112], and aflibercept[113] had good short-term safety and efficacy for new or recurrent VH in PDR eyes with and without a previously lasered approach, reducing the need for PPV. As the use of anti-VEGF drugs is associated with pregnancy loss and foetal abnormalities, PRP and PPV remain the treatment of choice for VH in pregnant patients with PDR. Surgery should be conducted under the assistance of an experienced anaesthetist to anticipate pregnancy-related anaesthetic complications[114].

Advances in PPV instrumentation have led to small-gauge vitrectomy increasing in popularity, improving the surgical experience, and allowing PPV to be performed under local anaesthesia. Nevertheless, surgical treatment of any kind is a form of stress during pregnancy. The supine position required for PPV may even prove challenging for pregnant patients due to the gravid uterus. Hence, this reiterates the need to stabilize PDR before pregnancy with a PRP laser and, if needed, PPV in diabetic patients. Although anti-VEGF has advantages, it cannot be used as a prepregnancy therapy for diabetic women with active PDR who are intending to conceive. This is due to the risk of conception loss when they subsequently conceive while treatment has to continue during pregnancy. If PDR progression occurs, surgical treatment should be delayed after delivery if this option is available.

Anaesthesia in the pregnant diabetic

Management of DR in pregnancy is essential, and preventing the development and progression of DR should be at all costs, as well as ensuring maternal and foetal safety. However, ophthalmic surgery during pregnancy poses additional challenges, which include the timing of the surgery, the posture during surgery, and the type of anaesthesia. Elective surgery is recommended to be postponed until 6 wk postpartum, while essential surgery should be performed in the second trimester if possible when preterm contractions and spontaneous abortions are least likely[115]. Pregnant women are susceptible to hypoxia, hypercapnia, and systemic hypotension due to altered maternal physiology, which exposes both the mother and the foetus to the risk of surgical anaesthesia, particularly general anaesthesia. Moreover, the supine position in the second and third trimesters can induce profound hypotension due to aortic and vena cava compression by the uterus. Pregnant patients should therefore be positioned with their hips, abdomen, and thighs on their left side while maintaining a normal head position for ophthalmic surgery[116].

Current anaesthetic medications, including general anaesthetics (nitrous oxide excluded), benzodiazepines, and opioids, have not been shown to have any teratogenic effects in humans when using standard concentrations at any gestational age[117,118] and have not been associated with increased rates of stillbirths or adverse pregnancy outcomes[119]. However, reports have shown an increased incidence of low birth weight and neural tube defects with exposure to general anaesthesia in the first trimester[120]; thus, general anaesthesia should be avoided whenever possible.

Local anaesthetics work by blocking sodium channels in nerve membranes, leading to absent nerve impulses and anaesthesia[121]. An extensive study on local anaesthetic use in 60000 pregnant females included benzocaine, procaine, tetracaine, and lidocaine and revealed no increased incidence of foetal complications[122] or foetal birth defects[123].

Under circumstances where general anaesthesia was necessary, an appropriate understanding of additional pregnancy-related risks should be considered, including intubation difficulties, aspiration risks, thromboprophylaxis, and foetal well-being[124]. General anaesthetics work at the level of the spinal cord and in different areas of the brain, which results in relaxation of the muscles and central nervous system depression, although the exact mechanism of action has not been ascertained[125]. Thiopentone in late pregnancy showed no significant effect on intrauterine pressure, while ketamine was found to cause a uterine contraction in early pregnancy and no effect in late pregnancy[126]. Volatile anaesthetics such as halothane, sevoflurane, desflurane, and isoflurane have been shown to inhibit uterine contractility; thus, they may be beneficial in preventing preterm contractions[127]. Nonetheless, the choice of anaesthetic technique and the selection of appropriate anaesthetic drugs should be carefully considered to preserve maternal safety, maintain the pregnancy state, and

achieve the best possible foetal outcome.

Screening for DR during pregnancy

According to Malaysia's Clinical Practice Guidelines: Screening of DR, individuals with pre-existing DM who are planning for pregnancy should have their eyes examined before conception and counselled on the risk of DR development and progression[128]. Subsequent follow-up is dependent on the stage of DR found on the initial examinations: Every 3 mo for mild to no DR and referral to an ophthalmologist is necessary for moderate to severe DR. Women with gestational DM (GDM) do not require DR screening, as it carries no risk of DR unless GDM is diagnosed in the first trimester of pregnancy. GDM is a glucose intolerance state induced by pregnancy that may resolve or persist after the pregnancy period[129,130], and the prevalence of GDM in Malaysia was reported to be approximately 8.8%[131]. Women with GDM have a sevenfold increased relative risk of progressing to T2DM[132-134], and they are usually asymptomatic until macular oedema or PDR has developed.

Bastion *et al*[135] reported a case of a 36-year-old pregnant woman who had GDM at her previous pregnancy with an elevated post-delivery maternal glucose tolerance test. Her first-trimester fundoscopy found no DR. By the second trimester, she had developed PDR, and PRP was performed on both eyes during her pregnancy. This was followed by PPV with membrane peeling in the right eye at five months postpartum, as the right VH did not resolve spontaneously, leaving her with counting-finger vision [135]. On the other hand, Raman and Livingstone reported a case study of a 31-year-old pregnant woman with underlying T2DM who had diffuse VH on both eyes at her 22nd week of gestation, which required urgent PRP. However, she developed recurrent VH in her third trimester, and PPV was then performed at 2 wk postpartum for her right eye, as it then developed inferior combined rhegmatogenous and tractional retinal detachment (TRD). Her left eye had a nonclearing VH requiring PPV a month later[136]. Both cases reported safe delivery of the baby and good postoperative visual acuity[135,136], highlighting the rapid progression of DR and the importance of follow-up and timely surgical intervention for a good final vision outcome.

However, Helen *et al*[137] reported four T1DM women with PDR who had adverse maternal outcomes, including abortion in one patient, preeclampsia, and preterm delivery in one patient, renal failure requiring dialysis in one patient, neonatal death occurring in one case, and premature delivery occurring in another case. All except one woman had stable or improved visual acuity. One woman progressed to develop neovascular glaucoma[137]. Hence, prepregnancy counselling and close follow-up during pregnancy and the postpartum period are essential for diabetic women.

The recommended ophthalmic management of DR during pregnancy at each stage [23,26] is summarized in the following flowchart (Figure 1).

Despite the best efforts to monitor and manage DR during pregnancy, the literature suggests that compliance with treatment and follow-up is still a struggle for pregnant women with diabetes. Hampshire *et al*[138] looked at attendance at a prepregnancy care program for adequate retinal assessment in the subsequent pregnancy and found that 70% of women with pregestational diabetes had incomplete follow-up[138], suggesting a lack of awareness on sight-threatening complications of diabetes[139].

CONCLUSION

There is limited evidence for the management of STDR in pregnancy, with evidence mainly from case reports and series. Management of STDR in pregnancy requires prepregnancy counselling, treatment, and stabilization of DM and STDR. It involves appropriate control of systemic risk factors for DR progression, monitoring of DR with fundus imaging at least every trimester, and prompt referral to the ophthalmologist when there is DR progression during pregnancy. Treatments that are conventional for DME, such as anti-VEGF, should not be given during pregnancy in diabetic patients, particularly in the early trimester, as there have been several reports of foetal loss. PRP can be given for severe NPDR and PDR; however, surgical management for VH or TRD in pregnancy should be deferred. If at all required, surgery should be performed under local anaesthesia, at an earlier trimester, or deferred until after delivery.

<p>PRE-CONCEPTION</p> <p>Pre-conception counselling addressing clinical modifiers (<i>e.g.</i> glycaemic control, hypertension and DR requiring treatment)</p> <p>Pre-conception fundus ophthalmic examination to determine DR stage prior to conception preferably a dilated fundus examination/at the very least a fundus photographic screening</p> <p>If STDR is detected, referral should be made to an ophthalmologist to ensure that treatment required is applied prior to pregnancy</p> <p>Contraception may be required if patient needs anti-VEGF</p> <p>Optimal glycaemic control</p>
<p>FIRST TRIMESTER</p> <p>Comprehensive eye examination includes photographic screening or dilated exam</p> <p>If severe NPDR or PDR progresses, consider PRP laser or if DME is detected consider grid or focal laser (Anti-VEGF not advised)</p> <p>Consider more frequent follow-up, even if vision is normal</p> <p>Control of risk factors for progression such as blood pressure, blood sugar level</p> <p>If blood sugar not controlled, initiate insulin therapy</p> <p>Consider more frequent eye follow-up if control is poor</p> <p>Review of risk factors for progression during poor glycaemic control, longer duration of diabetes and hypertension</p> <p>Consider more frequent follow-up</p>
<p>SECOND AND THIRD TRIMESTER</p> <p>Comprehensive eye examination includes photographic screening or dilated exam</p> <p>If severe NPDR or PDR progresses, consider PRP laser or if DME is detected, consider grid or focal laser</p> <p>Consider more frequent eye follow-up, even if vision is normal</p> <p>Control of risk factors for progression such as blood pressure, blood sugar level</p> <p>If blood sugar not controlled, initiate insulin therapy</p> <p>Consider more frequent eye follow-up if control is poor</p> <p>Review of risk factors for progression during poor glycaemic control, longer duration of diabetes and hypertension</p> <p>Consider more frequent follow-up if control is poor</p> <p>Anti-VEGF and surgery permissible if patient understands the risks (Deferment if possible)</p>
<p>POST-PARTUM</p> <p>Ophthalmic follow-up for DR/DME progression and complications</p> <p>Majority regressed post-partum</p> <p>Some may require PRP or PPV after delivery</p>

Figure 1 Flow chart showing the suggested management of sight-threatening diabetic retinopathy during pregnancy. DR: Diabetic retinopathy; STDR: Sight-threatening diabetic retinopathy; DME: Diabetic macular oedema; VEGF: Vascular endothelial growth factor; PRP: Panretinal photocoagulation; PDR: Proliferative DR; NPDR: Nonproliferative diabetic retinopathy.

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