



Management of diabetic retinopathy in pregnancy

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ABSTRACT

Introduction. The onset and development of diabetic retinopathy are more common during pregnancy. Pregnancy has no long-term effect on diabetic retinopathy; however, in 50-70% of cases, changes in retinopathy continues. The probability of worsening is highest in the second trimester and up to one year postpartum. Additional factors that have been associated with disease progression include duration of diabetes, the degree of retinopathy at the time of conception, management of hyperglycemia, anemia, and development of associated hypertension. In cases of severe non-proliferative retinopathy, it is recommended to promptly initiate laser photocoagulation rather than wait for early proliferative changes. Maintaining good diabetic control before and during pregnancy can help prevent disease progression and serious vision loss.

Material and methods. Diabetic retinopathy management in pregnancy was the subject of a comprehensive review of the scientific and medical literature. A structured search was performed in the PubMed, Scopus and HINARI databases, considering relevant articles published in the last 10 years. The search terms used (in English) were: „Diabetic retinopathy”; „pregnancy”; „laser photocoagulation”; „intravitreal steroids”; „anti-vascular endothelial growth factor”.

Results. It is suggested that women with diabetes receive pre-conception and post-pregnancy counselling from a multidisciplinary team including an ophthalmologist, endocrinologist, and perinatologist, as diabetic retinopathy may worsen during pregnancy. The risk of progression of the disease and the importance of appropriate metabolic control before and during pregnancy should be clearly explained to the patient. Careful monitoring is required in patients with advanced gestation, significant retinopathy, concomitant hypertension, and nephropathy.

Conclusion. The risk of retinopathy development may increase during pregnancy. Serious effects can arise for both the mother and the fetus, even though retinopathy is not common during pregnancy. It is possible to avoid significant retinopathy by carefully planning a young diabetic woman’s pregnancy and proceeding promptly to laser photocoagulate in cases of severe non-proliferative retinopathy. A tendency for regress is frequently seen in diabetic retinopathy during the post-natal period. Subsequent pregnancies do not significantly increase the risk of progression if the retinopathy is stable before pregnancy.

Keywords: Pregnancy; diabetic retinopathy; laser photocoagulation; anti-vascular endothelial growth factor; intravitreal steroids.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

The control of diabetic retinopathy is becoming more difficult due to the lack of information regarding the safety and effectiveness of existing therapy options during pregnancy.

The research hypothesis

When treating patients who already have diabetic macular edema, caution must be exercised in determining the necessity, timing, and level of therapy, as panretinal photocoagulation increases the risk of exacerbating the condition.

The novelty added by manuscript to the already published scientific literature

The recommended treatments for diabetic macular edema during pregnancy are intravitreal steroids or focal laser, if the condition responds to these measures. When treated with anti-VEGF medications, ranibizumab remains the preferred agent due to its shortened half-life and faster plasma clearance.

Introduction

Women with diabetes - regardless of the type of diabetes - must plan a pregnancy to ensure optimal conditions for the child's development and their own health and to reduce the risk of perinatal complications. The main problem with pre-existing diabetes is the development of diabetic embryopathy [1].

Pregnancy in women with manifest forms of diabetes primarily affects women with type 1 diabetes mellitus. However, recent surveys also show a continuous increase in type 2 diabetes mellitus, which, in addition to hyperglycemia, is complicated by obesity-related risks and often by older maternal age [2]. Even among pregnant women with diabetes type 1, a significant increase in BMI has been observed over the last decade. In both T1DM and T2DM, higher maternal BMI and higher blood pressure, in addition to metabolic control and diabetes duration at the start of pregnancy, were associated with poorer pregnancy outcomes. Migrant women and women from low socioeconomic backgrounds account for a significant proportion of women with diabetes type 2, particularly those who were inadequately treated and prepared for pregnancy or whose pre-existing diabetes was only newly discovered during pregnancy. Persistently poor pregnancy outcomes in women with pre-conceptual diabetes are also confirmed in recent population-based surveys [3].

Maternal obesity and inadequate metabolic control are the main modifiable risk factors, while maternal age, duration of diabetes and maternal deprivation are the main non-modifiable risk factors. No differences were found in congenital malformations and stillbirths between women with type 1 and type 2 diabetes, while premature births were more common in type 1 diabetes [4]. However, women with type 2 diabetes had a higher neonatal mortality rate. An HbA1C $\geq 6.5\%$ in the 3rd trimester, type 2 diabetes, and social disadvantage of the mothers were independent risk factors for perinatal death. Increased attention should be paid to achieve optimal glycaemia in women with type 2 diabetes before and during pregnancy, as these patients often already have additional cardiovascular risk factors, comorbidities, and the risk of complications is often underestimated [4].

According to The Diabetes Control and Complications Trial (DCCT), pregnancy increases the risk of retinal damage by 1.63 times compared to the state of the retina before pregnancy and by 2.48 times compared to similar indicators in non-pregnant women [5].

Potin *et al.* note that 61.2% of patients with type 1 diabetes mellitus and microvascular changes during pregnancy have DR. However, the occurrence or progression of DR is observed in 9.7% of pregnant women [6].

The worsening of DR during pregnancy is due to a number of factors: pregnancy itself, changes in retinal blood flow, inadequate glycemic control before and during pregnancy, the rapid normalization of blood sugar, the presence and severity of diabetic retinopathy before pregnancy, the duration of diabetes, the presence of hypertension, diabetic neuropathy, and pre-eclampsia [7].

The progression of DR depends considerably on the severity of glucose metabolism decompensation before conception and in the first 6-14 weeks of pregnancy, as well as the rate at which normoglycemia is achieved. The Diabetes in Early Pregnancy (DIEP) study revealed that 10.3% of women with DM1 who had an initial absence of ocular changes and progression of DR during pregnancy had baseline HbA1c level 4 standard deviations above normal. The DCCT study proved that the risk of DR progression in pregnant women with DM1 is directly related to baseline DM compensation [5].

B. Rosenn *et al.* note that patients with chronic hypertension or pregnancy-related hypertension have a higher frequency of diabetic retinopathy progression. Increased retinal blood flow, corresponding to the hyperdynamic circulatory state in pregnancy, can stimulate endothelial damage and become a significant factor in the progression of the condition [8].

There is a common belief that DR regresses in the postpartum period. The DCCT study indicated the transient nature of the changes occurring during pregnancy [5].

S. Arun and R. Taylor studied women with DM1 for 5 years after childbirth and found that pregnancy does not lead to long-term worsening of DR [9].

However, W. Chan *et al.* observed pregnant women with an aggressive course of DR and found that in this group of patients, in 81% of cases, the condition progressed to the proliferative stage in the postpartum period. Moreover, the most unfavorable outcomes in the form of traction and rhegmatogenous retinal detachment and neovascular glaucoma were observed when spontaneous regression of the disease was expected after delivery and timely retinal laser coagulation was not performed [10].

The progression of DR may depend on whether retinal laser photocoagulation was performed in the pregestational period. A study of patients with proliferative DR detected in early pregnancy who subsequently underwent laser photocoagulation showed progression and significant visual impairment in 58% of cases. In contrast, among patients in whom retinopathy was detected and treated before pregnancy, only 26% of cases showed progression of DR during the gestational period [11]. The indications for treatment and response to retinal laser photocoagulation in preg-

nant women are the same as in all patients with diabetes. Pre-conceptional stabilization of glycemia and blood pressure levels is of paramount importance to prevent the manifestation and progression of DR during pregnancy in diabetes. Glycated hemoglobin concentration should be maintained below 6.1% if possible and safe. It is important to monitor the ocular fundus throughout pregnancy - at least twice in different trimesters, as well as in the postpartum period until the process is completely stabilized. If progression of DR is detected, timely treatment, primarily retinal laser photocoagulation, improves visual prognosis [12].

Laser Treatment

It makes sense to advise close supervision in cases where a pregnant woman first develops moderate to severe diabetic macular edema, with a priority on achieving and maintaining adequate glucose control. Two diabetic individuals in the first trimester of their pregnancies were included in a Danish article. They had retinal edema 500–1500 µm in the fovea area. Good glucose management helped both patients improve, and as a result, they did not require any further care [13].

Although observation is a good choice for pregnant patients with mild to moderate diabetic macular edema (DME), it is important to observe these women more carefully than non-pregnant adults. If DME does not resolve after a period of follow-up, the first-line treatment option is laser treatment. The ETDRS reported that grid or focused laser treatment of clinically significant macular edema was successful in preventing continued visual disability [13, 14]. According to a study conducted in Copenhagen, two pregnant women diagnosed with type 1 DM and macular edema received targeted laser treatment and did not require any additional medical intervention during their pregnancy. When foveal involvement makes traditional laser therapy unsafe, subthreshold MicroPulse or endpoint management are two further options that could be taken into consideration. Following treatment using a MicroPulse laser, Italian researchers found a substantial short-term improvement in DME and visual acuity [15]. These non-invasive techniques might be useful in situations when traditional laser treatments are inappropriate or potentially dangerous, especially when a woman is newly pregnant [13, 15].

For pregnant patients with DR, panretinal photocoagulation is regarded as a reliable and effective therapy option. It has been shown to be an effective treatment for diabetic retinopathy during pregnancy and remains a vital treatment for stopping disease's progression. When administering PRP to pregnant people, proper scheduling is essential. According to recommendations, PRP therapy may be necessary for pregnant women at earlier stages, especially if their degree of DR approaches severe nonproliferative DR or higher [16].

Intravitreal Steroids in DME

There is little data in the literature on the use of intravitreal steroids during pregnancy, and much of the material available comes from modest research. A collection of research supporting intravitreal steroid usage and evaluation

of its safety profiles at different phases of pregnancy may exist, although it is not as extensive as the research supporting certain other therapies. It is critical to recognize the moral difficulties that arise when conducting extensive research on expectant mothers, as these challenges may limit the amount of high-caliber, widely available material. Because of the potential consequences for the developing baby as well as the mother, the safety of any medical intervention during pregnancy is a serious concern.

The use of intravitreal steroids during pregnancy should be decided on a case-by-case basis, carefully balancing the possibility of benefits versus any existing or prospective hazards, given the lack of information [13, 17].

Intravitreal Anti-VEGF Substances

Due to the lack of long-term efficacy evidence for anti-VEGF medication in pregnant patients, it is often used only as an emergency measure during gestation. Anti-VEGF medications, such as bevacizumab, ranibizumab and aflibercept are frequently used to treat a range of eye disorders, particularly retinal illnesses. Because the possible effects on the developing baby are a serious concern, pregnant women are frequently cautious about using drugs that have not been thoroughly investigated for their safety during pregnancy [18].

Consequently, anti-VEGF medication is usually considered only when alternative medical options are not possible or effective for a pregnant woman, and if it is determined that she needs it. Moreover, it is usually preferable to start anti-VEGF medication afterwards in pregnancy, especially in the third trimester. This period was chosen based on the idea of reducing possible hazards to fetal development during the critical early stages of pregnancy. In a patient with foveal-involving diabetic macular edema and a contraindication to steroids, the use of anti-VEGF therapy could be considered. The Diabetic Retinopathy Clinical Research Network study has shown that anti-VEGF therapies are highly effective in the treatment of DME. This study compared the outcomes of anti-VEGF therapy combined with laser treatment versus laser treatment alone. The drug's half-life in the plasma plays a role in deciding which anti-VEGF therapy to choose. Bevacizumab is known to have a longer half-life and to remain in the plasma for a longer period of time. Bevacizumab administered intravitreal has been demonstrated to lower plasma VEGF levels for a minimum of one month. Ranibizumab, on the other hand, has a shorter half-life and is cleared from the plasma quickly. Given that ranibizumab has a shorter half-life, it is considered a viable treatment option for expectant mothers and those who plan to become pregnant soon after receiving an anti-VEGF injection [13, 18, 19].

Women diagnosed with preproliferative DR during pregnancy should be counseled to attend regular eye examinations for at least 6 months postpartum and typically up to 1 year postpartum. This monitoring is important to track the progression of diabetic retinopathy and to ensure timely intervention if necessary. The DCCT study demonstrated that the higher risk of progression of DR during pregnancy per-

sisted for one year after delivery. Several of these women required laser photocoagulation for up to 12 months after delivery [20, 21]. Another study found that DR was more likely to progress 4 months after delivery than during pregnancy. This phenomenon may be related to the successful control of glycaemia during pregnancy, which then decreases in the postpartum period. Dilated funduscopy should be performed 1-2 months after delivery in those who had treated or untreated DME during pregnancy and in patients with mild, moderate or severe nonproliferative DR. This follow-up examination is recommended to assess the retinal status postpartum and should be continued until 12 months after delivery [22, 23].

Conclusions

Numerous factors affect how DR progresses throughout pregnancy, including the level of retinopathy at conception, the efficacy of medication, the duration of diabetes, the state of glucose regulation prior to pregnancy, and the existence of other vascular complications, such as associated or pre-existing hypertensive conditions. Retinopathy progression is less likely when risk factors are precisely identified, and diabetes is well managed. To protect the wellness of both the fetus and mother's eyes by improving early diagnosis and management of potential ophthalmic disorders, an ophthalmologist consultation is advised for women who have recently been diagnosed with diabetes during pregnancy.

The probability of vision loss is low for those who have mild retinopathy at the beginning of pregnancy; a fundus exam every three months is usually sufficient. Further regular evaluation is advised for patients with mild baseline retinopathy, with ophthalmoscopy carried out at each obstetrician visit. Investigations should be performed every two weeks if there are signs of progression. In situations where high-risk retinal modifications are suspected, laser photocoagulation should be performed immediately, with ophthalmoscopy used to monitor the process. Laser photocoagulation is recommended to be carried out before pregnancy or as soon as significant retinal alterations manifest in women with severe diabetic retinopathy [15, 23].

Competing interests

None declared.

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Ethics approval

Not needed for this study.

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