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Short Communication

Retinopathy in Diabetic Pregnancy-IGF and Progression

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Abstract

Retinopathy is of outmost importance in relation to conservation of the visual function and the quality of life. Diabetes mellitus is one of the main causes of blindness in the Western world. The mechanism by which pregnancy, diabetes, and retinopathy interact is by higher retinal flow and by circulating and vitreous IGF-1. Similar pathways may be suspected due to co-existence of vascular morbidity in the kidney and retina. Given the encouraging development of methods of diagnosing vascular morbidity, the aim is early to detect factors, which are responsible for further deterioration.

Key words:

Retinopathy; Pregnancy; IGF-1

Abbreviations

IGF: Insulin-like Growth Factor; IGFBP: Insulin-like Growth Factor Binding Protein; FGF: Fibroblast Growth Factor; ACE: Angiontensin Converting Enzyme

Introduction

Retinopathy is of outmost importance in relation to conservation of the visual function and the quality of life. Diabetes mellitus is the main cause of blindness in the Western world. The mechanism by which pregnancy, diabetes, and retinopathy interact is by higher retinal flow [1,2]and by circulating and vitreous insulin-like growth factor-1 (IGF-1) [3,4,5]. Similar pathways may be suspected due to co-existence of vascular morbidity in the kidney and retina. Given the encouraging development of methods of diagnosing vascular morbidity, the aim is early to detect factors responsible for further deterioration. The bulk of literature points to an overall adverse effect of pregnancy on diabetic retinopathy, which relates to diabetic risk factors [6,7]. In the largest prospective study on the subject to date, the incidence of progression of retinopathy is 6 % in the intensive treated group compared to 17 % of conventional treated group during pregnancy [7].

We find progression of diabetic retinopathy during pregnancy associated with a stepwise increase in serum total IGF-1 [8]. Further, we have co-authored findings on retinopathy associated with increased levels of fibroblast growth factor-2 (FGF-2) and phosphorylated insulin-like growth factor binding protein-1 (IGFBP-1) [9,10]. Similarly to others, we find tight metabolic control associated with less retinopathy (11,6,7].

The figures from the DCCT study cannot be extrapolated to the pregnancy situation due to difference in sex ratio and age but several pregnancy studies point to similar or higher incidences [12,13]. The DCCT study on pregnancy has some flaws in methodology as retinal exams are performed semi-annual i.e. only once or twice per pregnancy [7]. The study accounts for number of measurements and not patients, which biases the higher retinopathy grades with shorter examination intervals and repeated pregnancies. It is performed on retrospective capture of data on pregnancy and the numbers of retinal data in the two treatment groups are heavily disproportional [7]. Nevertheless, women have similar end points irrespective of pregnancy and they end up with similar retinopathy levels after 6.5 years of follow-up [6]. Taken together, regression of diabetic retinopathy after pregnancy is common and this may impair the assessment of the risk of persisting retinopathy [13].

IGF-1

Since it was shown that pituitary ablation could halt proliferative diabetic retinopathy, focus is on the gestational changes in growth stimulating hormones [4,14]. Postoperatively, the IGF-1 levels decreases sharply in accordance with the role of IGFs promoting mitosis and growth of the retina and vitreous [4,15,16].

Women with proliferative retinopathy have elevated HbA1c levels that are associated with higher IGF-1 in non-pregnant, diabetic subjects [9,12,13]. However, we fail to confirm such an association of glycemia with IGF-1 during pregnancy in women with proliferative retinopathy [1,8]. However, we did find a relation of increase in circulating IGF-1 with progression from any stage of diabetic retinopathy with use of standardized and blinded assessment [8] [Figure1]. The gestational change of IGF-1 levels may in part explain previous conflicting reports on correlation with retinopathy [5,17-20].

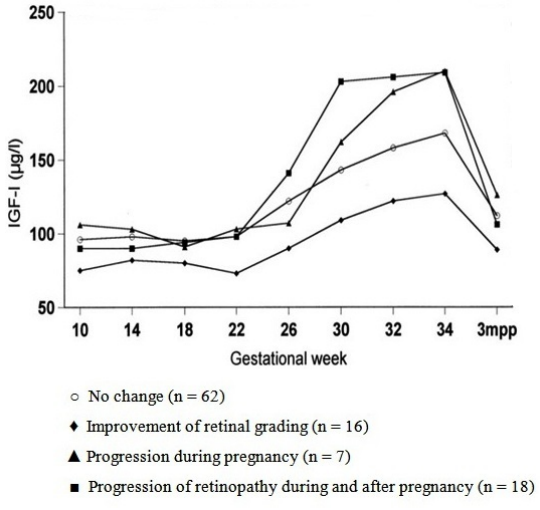

Figure 1: IGF-1 in relation to change of retinal grading. 3mpp - 3 months postpartum, P < 0.01 for all groups, weeks 14–34, two-way ANOVA

Our findings extend previous observations suggesting a possible role of elevated serum IGF-1 for accelerating diabetic retinopathy during pregnancy [8, 5,15,16,18]. We find an association of increase in IGF-1 with progression of diabetic retinopathy despite good glycemic control in pregnancy. Whether the new insulin analogues can improve the situation has yet to be established [21,22,23,24]. We co-report that retinopathy in pregnancy is associated with elevated levels of FGF-2 and highly-phosphorylated IGFBP-1. The latter further increases the level of free IGF-1 as well as FGF-2 [9,10]. Thus, the effect on development of retinopathy may be directly mediated by IGF-1 or indirectly by a modifying effect of IGFBP-3 and phosphorylated isoforms of IGFBP-1 [25-27, Figure2 and Figure3]. Loukovaara et al cannot corroborate the finding, but they include diabetic women with nephropathy (24 % of their study population) and moderate retinopathy (12 %) [1]. They have only two points of measurements during pregnancy and a substantial number of non-compliances or non-attendees (21 out of 63). The final analysis, thus, may include some bias. We conclude that in diabetic pregnancy most evidence support the association of IGF-1 with progression of retinopathy

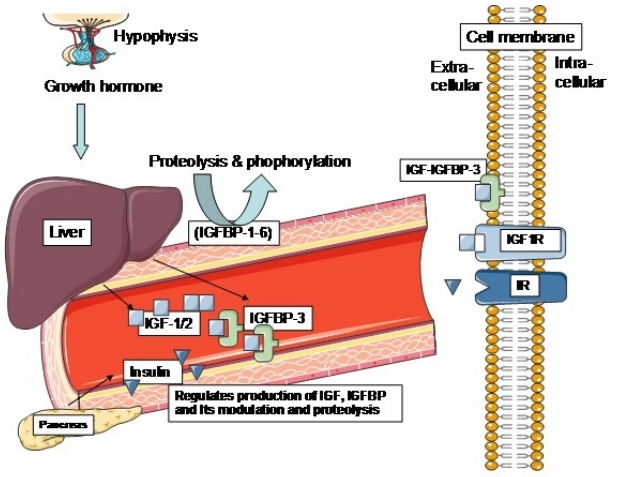

Figure 2: IGF physiologyIGF secretion and binding in extracellular space by its receptor (IGF1R) and IGFBPs. IGFBPs are modulated by proteolysis and phosphorylation. Insulin binds to insulin receptor (IR)

The largest study to date in non-pregnant subjects, the population-based Wisconsin study, finds no relationship with IGF-1 and retinopathy. However, half of their subjects have older-onset, possibly type 2 diabetes mellitus. Further, those who progress to proliferative retinopathy within the first 4 years are excluded, leaving a little more than half the original number of subjects to be studied [17]. Further, IGF-1 is measured at baseline, six years before the retinal evaluation at follow-up. No further IGF-1 data were presented. As the data on IGF-1 are prevalence and not incidence data, the design is not satisfactory. The lack of associations between IGF-1 and retinopathy could be explained by potential undetected confounding during the observations period [28].

In non-pregnant, diabetic women the association of serum IGF-1 and retinopathy is not consistent and non-conclusive. One study show lower free IGF-1 levels in type 1 diabetic patients with retinopathy compared with patients without retinopathy; other studies yield the opposite result [3,4,15,16,19,20]. Several studies conclude that free IGF-1 measurements have no advantage compared to total IGF-1 [3] and that age is an important confounder [20]. Another study on the vitreous body concludes that intraocular synthesis of IGF-1 is responsible for progressive retinopathy while unspecific increase of intravitreal proteins is the main factor for the elevated levels of IGFBP-1 and IGFBP-3 in the vitreous body [29,30].

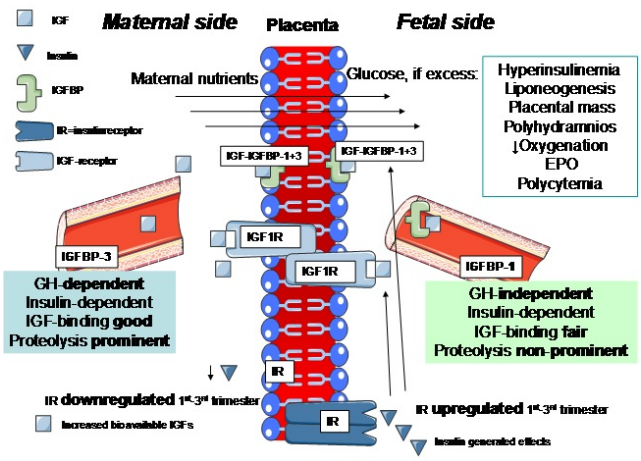

Figure 3: Effects of pregnancy on the IGF system, including hyperglycemia. Inserted boxes show (from top to bottom, left to right) effects of hyperglycemia on the fetus, pregnancy's effect on IGFBP-3 and IGFBP-1, the two key regulating binding proteins of IGFs on the maternal and fetal side, respectively. IR: Insulin receptor

Glycemic control

Large prospective studies in non-pregnant diabetic subjects have all pointed to the beneficial effect of intensive control on glycemia and hypertension, which seems plausible for pregnancy as well. In the DCCT study, pregnancy per se does not increase the risk of worsening of retinopathy while hyperglycemia has a major impact [7]. Its evaluation includes 180 women in total. Despite methodological caution the DCCT study on pregnancy is categorized as a quasi-randomized study. The largest European cohort study in 2005 finds similar associations of glycemic regulation and retinopathy. 102 pregnant women were enrolled with a follow-up of 6-8 years [31]. HbA1c, duration of diabetes, and pre-pregnancy retinal state all affect the risk of progression of retinopathy whereas pregnancy did not. We found in a prospective series of 124 women no association of progression of retinopathy during and 6 months after pregnancy [11]. The above-mentioned finding of an association between increasing serum IGF-1 and progression of retinopathy may reflect effects by the pregnant condition per se when decreasing insulin sensitivity is present [32]. Therefore, we conclude that the initial glycemic regulation and HbA1c during pregnancy plays a leading role for progression of retinopathy

Macrosomia

The association between serum IGF-1 and progression of retinopathy may reflect a growth stimulus induced by pregnancy and may act on retinal neovascularization as well as on birth weight

[8,15,16]. This view is supported by the finding of progression of retinopathy associated with reduced fetal growth [32]. Adjustment for hypertension and nephropathy was performed but may still have confounded the results as they constituted for 40 and 20 %, respectively. In our prospective retinopathy study we find an association of IGF-1 with macrosomia despite only rare progression of retinopathy. Thus, strict glycemic control may achieve its goal on retinopathy easier than fetal growth.

The question is whether unrecorded smaller exacerbations on glycemia may still exert their effect on fetal growth or whether newer insulin analogues improvement together with continuous glucose measurements benefit pregnancy outcome [33-39].

Albumin excretion rate

Diabetic vascular complications are unanimously associated what seems to be the case in retinopathy and increased albumin excretion rate [40,41]; our clinical experience shows that in some patients retinopathy does not necessarily include or preclude nephropathy. Although superficially similar the hyperpermeability in retinopathy and nephropathy exhibits important differences: The pathophysiology of micro- and macroalbuminuria is hyperpermeability with albumin excretion between podocytes and loss of negatively charged proteoglycan, which otherwise would hold albumin back; maculopathy, too, is characterized by hyperpermeability, though, with no excretion but with leakage of lipoproteins and fluid giving rise to formation of hard exudates and edema in the retina. Proliferative retinopathy occurs when growth of vessels compensates for local ischemia. These clinical observations in different organs, in turn, may be influenced by the same or similar factors. These may vary in their effect in different organs or the patient's susceptibility to adverse events.

Blood pressure

In general hypertension gives rise to retinal changes that are partially reversible once treatment has commenced. In diabetes the vascular retinal permeability is increased and pregnancy adds to the phenomenon. Prospective studies in diabetic subjects show that the systolic blood pressure is a predictor for development of retinopathy whereas diastolic blood pressure is related to the progression of retinopathy [42,43]. These relationships in type 1 diabetes are not consistent as glycemic control and albumin excretion rate are stronger correlates. Most studies in diabetic pregnancy find good glycemic control decreases risk of retinopathy. The aim of blood pressure treatment is to spare renal function and to prepare for delivery to improve obstetrical outcome. Surprisingly, only a few randomized trials are performed with the primary endpoint of evaluating effects of antihypertensive treatment on retinopathy in diabetic, non-pregnant subjects [44,45]. As evidence-based treatments involve ACE inhibitors and angiotensin receptor antagonist their practical value remains limited as these drugs are not even recommendable in pregnancy. Further, the trials find effect on the incidence of retinopathy but fail to show similar effect on progression, indicating that there may be a 'point of no return' for effects by medical treatment of blood pressure.

In conclusion, the associations of retinopathy with IGF-1, albumin excretion rate, blood pressure, and macrosomia may vary due to glycemia, the different background population studied, and the varying natural history of retinopathy during pregnancy and in the time immediate after delivery.

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