·Clinical Research·

Correlation of serum insulin like growth factor -I with retinopathy in Malaysian pregnant diabetics

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Received:2010-10-21 Accepted:2010-12-01

Abstract

• AIM: To study the association of serum insulin-like growth factor-I (IGF-I) with diabetic retinopathy.

• METHODS: Serum IGF-1 levels were measured in 25 pregnant diabetic patients and 25 pregnant non-diabetic patients who were matched for age, ethnicity, parity and period of gestation. Fundus examination was performed in both groups at 28, 32 and 36 weeks of gestation.

• RESULTS: The serum IGF-I level was significantly elevated in pregnant diabetics compared to pregnant non-diabetics (366± 199μg/L *vs* 184± 89μg/L, (P=0.0001) at 24 weeks, 535± 251μg/L *vs* 356± 89μg/L, (P=0.007) at 32 weeks and 404± 166μg/L *vs* 264± 113μg/L, (P=0.003) at 36 weeks of gestation). The pregnant diabetics with established diabetes had significantly higher IGF-1 level than that gestational diabetes at 28, 32 and 36 weeks of gestation. The serum IGF-I level in pregnant diabetics with retinopathy was significantly higher than in those without retinopathy at all periods of gestation.

• CONCLUSION: Increased serum IGF-1 in pregnancy may increase the risks for retinopathy.

• KEYWORDS: diabetic retinopathy; pregnancy; serum IGF-1 level
DOI:10.3980/j.issn.2222-3959.2011.01.16

Adzura S, Muhaya M, Normalina M, Zaleha AM, Sharifa Ezat WP, Tajunisah I. Correlation of serum insulin like growth factor-I with retinopathy in Malaysian pregnant diabetics. *Int J Ophthalmol* 2011;4 (1):69-72

INTRODUCTION

In Southeast Asia, the prevalence of blindness has been reported to be 1.2% in Indonesia, 1.1% in Thailand and 0.8% in Vietnam [1]. The prevalence of blindness among the Malaysian adult between the age of 30 and 70 was 0.29%, with 14.6% due to diabetic retinopathy [2]. In pregnant diabetic women, the prevalence of diabetic retinopathy is high, ranging from 10% to 27% . Based on the Diabetic Control and Complication Trial Research Group (DCCT) results, pregnant diabetic women has a 1.63-fold greater risk of any worsening of retinopathy from before to during pregnancy in the intensive treatment group, the risk was 2.48-fold greater for pregnant *vs* non pregnant women in the conventional group [3]. The retinopathy progresses markedly among the IDDM and NIDDM compared with gestational diabetes. Diabetic retinopathy is known to progress during pregnancy but the exact mechanism is still unknown. Clinical evidence has suggested that Insulin-like Growth Factor (IGF) system may be involved in the development of retinopathy in pregnancy. Elevated vitreous and aqueous IGF-I levels are strongly linked to proliferative diabetic retinopathy and other neovascular disorders secondary to retinal ischemia[4]. Lauszus *et al* [5] showed that despite good glycemic control in pregnancy, an increase in circulating IGF-I takes place concomitantly with progression of diabetic retinopathy. This is possible because serum and vitreous IGF-I concentration have been shown to correlate, probably due to leakage of IGF-I from the blood stream. This study is undertaken to compare the level of serum IGF-I between pregnant diabetic patients (DP) and pregnant non-diabetic patients (NDP) at different periods of gestation during the third trimester. In this study, we also measured the level of serum IGF-I in pregnant women with established diabetes (NIDDM and IDDM) compared to those with gestational diabetes. Since the level of serum IGF-I have been shown to be high in pregnant women with diabetic retinopathy, we also studied the significance between diabetic retinopathy and serum IGF-I level in pregnant diabetics.

MATERIALS AND METHODS

Materials This case-controlled, prospective study included patients with established diabetes, gestational diabetes and non-diabetics attending the Obstetrics and Gynaecology Clinic, National University of Malaysia from Jan. 2004 to Jan. 2005. Patients meeting the inclusion criteria were included into this study and they were selected based on method of universal sampling. Pregnant women with established diabetes and/or gestational diabetes mellitus were included in the study. Established diabetes is defined in a woman who becomes pregnant and who is known to have diabetes mellitus (IDDM or NIDDM), which antedates the current pregnancy. Gestational diabetes mellitus is a carbohydrate intolerance resulting in hyperglycemia of variable severity with onset of first recognition during pregnancy. It is diagnosed by oral glucose tolerance test (OGTT) within gestational age of 28±2 weeks and 36±2 weeks. Any pregnant woman who meets WHO criteria for diabetes mellitus or impaired glucose tolerance is classified as having gestational diabetes mellitus. Normal, non-diabetic pregnant women (NDP), age, ethnicity and parity matched at third trimester within gestational age of 28±2 weeks and 38± 2 weeks were taken as the control group. Any patients with previous history of laser treatment; with concurrent other endocrine problems such as hyperthyroidism and hypertension; with ocular pathology such as glaucoma, high myopia (more than -6D) and cataracts; with end stage renal failure and nephrotic syndrome were excluded. Informed consent was obtained from all patients upon ethical committee clearance, and the study was conducted in accordance with the Declaration of Helsinki and subsequent revisions thereof. Based on these two criteria, a total of 50 patients were examined which included 25 pregnant diabetics (DP) (established diabetes and gestational diabetes) and 25 pregnant non diabetic patients (NDP) who were matched according to age, ethnicity, gestation and parity. There was no significant difference in mean age (P=0.4), ethnic distribution (P=0.79) and parity status (P=0.24) between the DP and NDP groups. There were 21 (42%) Malays, 21 (42%) Chinese, 5 (10%) Indians and 3 (6%) patients from other races. The mean age of patients was 31.56±6.32 years in DP group and 29.44±3.94 years in NDP group. Out of the 25 patients in DP group, 17 (34%) were established diabetics (Type 2 diabetes, n= 5 and Type 1 diabetes, n=2), and 8 (16%) patients were gestational diabetics. Seven patients were primigravida (14%) and 18 (36%) were multigravida. In NDP group, 9 (18%) patients were primigravida and 16 (32%) patients were multigravida. In DP group, the duration of diabetes mellitus was between 1 to 18 years with a median of one year. Among the established diabetics group, there were 2 out of 17 patients detected to have diabetic retinopathy at first fundus examination at 28 weeks of gestation and both of them were IDDM. The first patient had asymmetrical diabetic retinopathy changes where she developed proliferative retinopathy in the left eye and mild non-proliferative changes in the right eye. She had 10 years history of IDDM (since age of 16 years) where the diabetes was poorly controlled. Pan retinal photocoagulation (PRP) treatment for the left eye was given over four sessions with a total number of 2569 burns. She unfortunately developed two episodes of vitreous haemorrhages in the left eye during the third trimester despite laser PRP. In view of the poorly controlled diabetes, an emergency lower segment caesarean section (LSCS) was performed at 36 weeks gestation. She gave birth to a healthy baby boy with a birth weight of 3.4kg. One month after delivery, visual acuity of the left eye improved to 6/9 and fundus examination showed a left quiescent proliferative diabetic retinopathy.The second patient with retinopathy in the established diabetes group had mild non-proliferative changes in both eyes. She had 8 years history of IDDM (since age of 16 years). In contrast to the first patient, her diabetes was well controlled during her pregnancy. She gave birth to a healthy baby girl with a birth weight of 3.6kg via spontaneous vaginal delivery. Two months after delivery, the fundus examination showed no progression of her retinopathy bilaterally.

Methods All patients who fulfilled the inclusion criteria underwent examination at 28 weeks of gestation that consisted of height, weight and blood pressure measurement, assessment of best corrected vision acuity, followed by slit-lamp biomicroscopic examination and intraocular pressure reading. The pupil was dilated with tropicamide 10g/L and phenylephrine 25g/L eye drops. Fundus was examined by indirect ophthalmoscopy and posterior pole examination was performed with 90 diopter lens when necessary. Fundus photography was performed with Topcon Retinal Camera TRC-50IX with Image Net Digital Imaging System. The retinopathy was graded and findings were entered in the data collection sheet. The fundus examination was repeated at 32 weeks and 36 weeks of gestation. The patients' blood samples were taken using 21G needle; 3mL of blood was syringed out from each patient for measurement of IGF-I during each visit. The blood was centrifuged to separate the serum from other components using the centrifuge machine at the rate of 3000r/min for 10 minute duration. The sample was than kept in the freezer at -20℃ until adequate sample amount was available for analysis. IGF-I was measured using Automated Chemiluminescent Immunoassays on the IMMULITE® machine analyzer[6].

This technique was compatible with Nichols Advantage™ assay for serum IGF-I level measurement[7].

Statistical Analysis The difference in mean of serum IGF-I between DP group and NDP group and between pregnant women with diabetic retinopathy and pregnant women with no diabetic retinopathy was tested using Mann-Whitney *U* test. The difference in mean of serum IGF-I level between established diabetes and gestational diabetes groups was tested using Kruskal-Wallis test. The association between diabetic retinopathy and IGF-I level was tested using Chi square with Fisher's exact test. $P<0.05$ was considered statistically significant.

RESULTS

Serum IGF -1 in DP and NDP There was statistically significant difference in serum IGF-1 level between DP group compared to NDP group (366±199μg/L *vs* 184±89μg/L, $P=0.0001$) at 24 weeks, (535±251μg/L *vs* 356±89μg/L, $P=0.007$) at 32 weeks and (404±166μg/L *vs* 264±113μg/L, $P=0.003$) at 36 weeks of gestation. There was significant increase in serum IGF-I level from 28 to 32 weeks followed by significant decline of serum IGF-I level from 32 to 36 weeks of gestation (0.0001 in both groups).

Serum IGF -1 between established diabetes and gestational diabetes The diabetic pregnant (DP) group was further divided into established diabetes ($n=17$) and gestational diabetes mellitus ($n=8$). There was a statistically significant difference in serum IGF-I level between established diabetes and gestational diabetes (392±217μg/L *vs* 311±153μg/L, $P=0.01$) at 28 weeks, (558±278μg/L *vs* 498±175μg/L, $P=0.025$) at 32 weeks and (416±184μg/L *vs* 377±130μg/L, $P=0.012$) at 36 weeks of gestation.

Serum IGF -1 in DP with *vs* without diabetic retinopathy There was statically significant difference in serum IGF-1 level between pregnant diabetic patients with diabetic retinopathy compared to pregnant diabetic patients with no diabetic retinopathy(541±267μg/L *vs* 264±169μg/L, $P=0.03$) at 28 weeks,(937.5±112μg/L *vs* 425±184μg/L, $P=0.000$) at 32 weeks and (645±282μg/L *vs* 322±141μg/L, $P=0.004$) at 36 weeks of gestation. However, There was no positive association between diabetic retinopathy and serum IGF-I level at different periods of gestation (at 28 weeks ($P=0.49$), 32 weeks ($P=0.225$) and 36 weeks of gestation ($P=0.49$) (Table 1).

Table 1 Outcome cross tabulation of serum IGF-I pregnant diabetic women ($n=25$)

Gestation period (Median, μg/L)		Diabetic retinopathy		
		Yes	No	
28 weeks	<224	0	25	25
	>224	2	23	25
32 weeks	<404	0	25	25
	>404	2	23	25
36 weeks	<336	0	25	25
	>336	2	23	25

DISCUSSION

The major finding in this study was a significantly higher difference in serum IGF-I level in pregnant diabetic group compared to pregnant non-diabetic group during the third trimester of pregnancy. Serum IGF-I in pregnant diabetic group was doubled compared to pregnant non-diabetic group at 28 weeks of gestation, with 1.5 fold increases at 32 and 36 weeks of gestation. Interestingly, the pattern of serum IGF-I level showed a significant rise from 28 weeks to 32 weeks gestation in both groups before showing a significant decline from 32 weeks to 36 weeks gestation in both groups. The pattern of serum IGF-I rise observed in this study is similar to another study by Hayati *et al* [8] who documented a significantly higher concentration of serum IGF-I in diabetic pregnancy compared to controls, both at 28 and 36 weeks of gestation. Lauszus *et al* [7] also reported similar serum IGF-I pattern changes, where the level was increased with increased gestational age until a plateau is reached at 34 weeks of gestation followed by a decrease from weeks 36 to 38 and full normalization after delivery.

The pathophysiology for deranged serum IGF-I in pregnant diabetics is explained by the role of human placental growth hormone (hPGH) which gradually replaces the pituitary growth hormones from week 20 onward. Production of maternal IGF-I is regulated by placental hormone *via* hypothalamic-growth hormone-IGF I axis. The pituitary growth hormone regulates the secretion of IGF-I, which, in turn, exerts negative feedback action on growth hormone at hypothalamic pituitary level. During the latter half of pregnancy, the growth hormone-IGF-I axis is inhibited by large amount of oestrogen. The larger increase in placental growth hormone exerts an inhibitory effect on growth hormone secretion mediated by placental growth hormone on the hypothalamus and pituitary. The hPGH is secreted by placenta into the maternal circulation and stimulates maternal IGF-I production in the liver. IGF-I level do not vary significantly during the first weeks of gestation, but then increase gradually from 165±445mg/L at about 24-25 weeks of gestation, and reach levels of 330.5±63.5mg/L at 32 weeks of gestation. Increase in maternal serum IGF-I will result in development of insulin resistance during pregnancy followed by hyperglycemia towards the second and third trimester. In diabetic pregnancy, there is further increase in the production of maternal serum IGF-I through stimulation of IGF-I mRNA from the term placenta. This excessive production of maternal serum IGF-I production is part of adaptive response of the adverse environmental such as

hyperglycemia in pregnancy complicated with diabetes.

Based on the above observation, measuring serum IGF-I in third trimester may help us to identify pregnant women who are at a risk of developing diabetes in pregnancy especially those who belong to high risk groups such as over weight, strong family history of diabetes, previous history conceiving and delivering a big baby and previous history of congenital malformation.

Gestational diabetes is defined as glucose intolerance that begins or first detected during pregnancy. The WHO oral glucose tolerance test (OGTT) criteria is the most commonly used to diagnose this condition [9]. Debates continue as to whether gestational diabetes represents a pregnancy-induced state of glucose intolerance or a state of pre existing insulin resistance that would become evident in the future regardless of pregnancies. There are many similarities between gestational diabetes and the syndrome of insulin resistance in non pregnant subjects [9]. Since this study had shown that IGF-I was higher in established diabetes group compared to gestational diabetes, it could be proposed that both the combination of serum IGF-I and the WHO OGTT criteria could be used to differentiate true gestational diabetes from chronic diabetics who become pregnant whom are mistakenly labelled as gestational diabetics. Thus, proper screening prior to pregnancy or while planning for pregnancy is important so as not to miss the group of people who are asymptomatic prior to pregnancy. This study also showed that the serum IGF-I level in pregnant women with diabetic retinopathy was significantly higher compared to those with no diabetic retinopathy. Lauszus *et al* [7] and Rozita *et al* [5] also supported this finding where they found a significant rise in serum IGF-I among diabetic patients with diabetic retinopathy compared with diabetic patients without diabetic retinopathy. It has been hypothesized that a rise in serum IGF-I level may be related to vascular microangiopathy and risk of end organ damage development such as diabetic retinopathy and diabetic nephropathy. The pathophysiology behind this microangiopathy was observed in a study by Grant *et al* [8] who reported a high IGF-I level in the vitreous body of diabetic patients with diabetic retinopathy compared to non diabetic patients. That study also suggested that serum and vitreous IGF-I concentration were related probably due to leakage of IGF-I from blood stream. Cummings *et al* [9] reported a strong association between urinary IGF-I and microalbuminuria in patients with type 1 diabetes. The same study also found a significant correlation between plasma IGF-I and urinary IGF-I in type 1 diabetes patients. Based on this, one could postulate that in clinical setting, measurement of serum IGF-I may be able to predict those pregnant diabetics who are at high risk of developing diabetic retinopathy and other end organ damage due to diabetic microangiopathy. In the future, it is hoped that IGF-I may serve, like VEGF, as a potential therapeutic target for the treatment of intraocular neovascularization especially in diabetic retinopathy. However further studies and clinical trials are required to achieve this. This study has shown that the mean serum IGF-I level is elevated in diabetic pregnancy compared to non diabetic pregnancy during the third trimester and that the level was markedly higher in pregnant diabetics with diabetic retinopathy. Thus it is recommended that women who are planning for pregnancy should undergo proper diabetic screening since increased levels of IGF-1 in the pregnant state may increase the risks for diabetic retinopathy which is a major visual morbidity.

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