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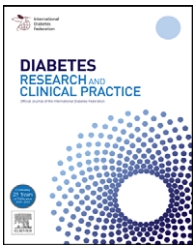

Microvascular complications are associated with low levels of maternal sE-selectin and sVCAM-1 in pregnancy complicated with pregestational diabetes mellitus

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ABSTRACT

Pregestational diabetes with vasculopathy in pregnant women is still associated with increased risk for severe maternal and foetal complications and their pathomechanism remains unclear. We investigate endothelial function in diabetic pregnant women with and without vascular disease, measured as changes in concentrations of soluble E-selectin and VCAM-1 throughout pregnancy. 121 pregnant women with PGDM and singleton pregnancy (30 participants with vasculopathy, 91 without vasculopathy) were enrolled into the prospective study. Control group consisted of 20 nondiabetic pregnant women in uncomplicated gestation, sampled cross-sectionally in early pregnancy and at term. We demonstrated lower concentrations of circulating sE-selectin both in early and in late diabetic gestation, irrespective of a concomitant vasculopathy. We also found reduced concentrations of sVCAM-1 in late gestation in diabetic pregnancies both with and without vascular disease, and reduced increase in its levels with gestation. We report significantly elevated concentrations of sVCAM-1 in early pregnancy in diabetic participants with retinopathy and nephropathy comparing with patients with retinopathy only and nondiabetic pregnant controls. We noted a general pattern of pregestational diabetes associated with reduced levels of cell adhesion molecules in early pregnancy with a further reduction during gestation, except for participants with combined retino- and nephropathy.

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1. Introduction

Despite a significant improvement in perinatal outcome noted during last decades, pregnancy complicated with pregestational diabetes (PGDM) still remains a high risk pregnancy. Incidence of foetal malformations and miscarriages continues to be 3 up to 4-fold higher in this population comparing to healthy women [1,2]. Also severe conditions like maternal hypertension, preeclampsia, placental insufficiency and fetal growth abnormalities are seen much more frequently in diabetic pregnancy [3–6]. In infants born to women with PGDM, prematurity, perinatal injuries, admissions to Intensive Neonatal Care Units and metabolic abnormalities – particularly hypoglycaemia, erythremia and hyperbilirubinemia (together with excessive birth weight referred to as "diabetic fetopathy") – are major reasons for suboptimal perinatal outcome [7]. Moreover, there is an increasing amount of data accumulated on a connection between an *in utero* exposition to maternal hyperglycemia and increased risk of remote diabetes and cardiovascular disorders in later life of offspring born to mother with PGDM [7]. Microvascular complications typical for a long history of diabetes – diabetic retinopathy and particularly nephropathy – constitute another risk for pregnant women as they may affect gestation course and perinatal outcome. Moreover, it is still open for discussion whether pregnancy itself has a negative impact on progress of

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diabetic vascular disease and available data is often confusing [3,8,9]. As all these complications are frequent also in metabolically well-controlled population, further studies on their pathomechanisms are necessary.

Recently, a possible impact of vascular endothelial function on development of chronic microvascular complications has been intensively studied [10–13]. Increased levels of markers of endothelial dysfunction have been reported as predictive factors for diabetic retinopathy and nephropathy [14,15]. Some studies also demonstrated elevated levels of cell adhesion molecules in a population at higher risk of type 1 or type 2 diabetes [16].

There is only scarce data on endothelial dysfunction in diabetic pregnancy. In their study, Ang et al. described impaired response to endotelin-1 in a small group of pregnant women with T1DM compared to healthy controls [17]. In another study, higher concentrations of sVCAM-1 were found in small groups of pregnant women with different gestational complications (HELLP syndrome, pregnancy-induced hypertension, pre-eclampsia and diabetes) compared to normal controls [18]. Raynor and Parthasarathy investigated changes in sVCAM-1 levels during normal pregnancy in 78 healthy individuals, reporting a mild decrease in this cell adhesion molecule's concentrations throughout gestation [19]. A study of Krauss et al. showed that concentrations of sVCAM-1 and sICAM-1 assessed between 22nd and 29th week of normal gestation may be useful predictors for further complications (mainly gestational diabetes and pregnancy-induced hypertension) [20]. Pertyńska et al. investigated cell adhesion molecules present on neutrophils as receptors and found enhanced expression of these molecules both in pregnant women with DM and in healthy pregnant controls, compared to healthy nonpregnant women [21].

In this study, we aimed at analysis of circulating plasma concentrations of soluble E-selectin (sE-selectin) and vascular cell adhesion molecule-1 (sVCAM-1) in pregnant women with PGDM, with or without microvascular complications (retinopathy or nephropathy).

2. Subjects and methods

Our study group consisted of 121 pregnant women with type 1 diabetes mellitus in singleton pregnancy (30 participants with vascular disease, 91 without it) covered with a tertiary-level perinatal care in the Department of Obstetrics and Women's Diseases between 2001 and 2005.

All participants were offered a treatment following the protocol adopted in our Department including periodical hospitalisations and check-ups in our outpatient clinic.

During the first visit in the Department, a gestational age and number of fetuses was confirmed in vaginal ultrasound examination, all participants had their metabolic control checked and participated in a training on blood glucose self-control, insulin therapy, diet and lifestyle. All individuals were treated with human insulins or rapid acting analogues using the basal-bolus protocol. Doses were adjusted following records from personal glucometers (taken 4–6 times a day). Fasting glycemia between 60 and 90 mg/dL and 2-h postprandial glycemia after main meals below 120 mg/dL was taken as a target value.

In all participants from the study group data from general and obstetrical history was taken as well as maternal history of diabetes: patient's age at onset, duration of the disease and the presence of the vascular disease before pregnancy. During each hospitalisation (once a trimester), HbA_{1c} and average daily glycemia were measured and blood pressure monitored.

Participants with nonproliferative or proliferative retinopathy diagnosed prior the pregnancy or during the first antenatal visit in the Department or with photocoagulation in their history were defined as patients with retinopathy. All participants had their eyes examined by ophthalmologist once a trimester. In 7 cases, a gestational progression of retinopathy was diagnosed (from nonproliferative to proliferative retinopathy or photocoagulation during pregnancy was necessary).

In all participants following indicators of renal function were measured once a trimester: serum creatinine and urea level, GFR, urinary protein excretion (from daily urine collection). According to White classification, individuals with prepregnancy diagnosis of diabetic nephropathy or with daily protein excretion exceeding 0.3 g/24 h (macroalbuminuria) and no symptoms of urinary tract infection at booking were defined as patients with nephropathy. In 3 cases, a gestational progression of renal disease (proteinuria found in examination at IInd or IIIrd trimester) was found.

Biochemical parameters were measured in Central Laboratory of the University Hospital that is a certified unit meeting the criteria of ISO 9001. At the first and final visit, in all subjects additional blood sample was drawn from antecubital vein after overnight fast, centrifuged, plasma aliquoted and stored in $-70\,^{\circ}C$ until assayed for cell adhesion molecules concentrations.

Levels of sE-selectin and sVCAM-1 were measured using the quantitative enzyme immunoassay technique (Quantikine® for human sVCAM-1, Parameter for human sE-selectin, R&D Systems, Inc., Minneapolis, MN, USA), following the manufacturer's protocols. The minimum detectable concentration was less than 0.1 ng/mL for sE-selectin and less than 1.26 ng/mL for sVCAM-1.

The control groups consisted of 20 healthy, age-matched pregnant women sampled cross-sectionally at 8–12 and 37–39 weeks' singleton, uncomplicated gestation. Average age in the control group was 30.0 ± 5.5 years.

All participants gave an informed consent and study protocol obtained approval from the Ethics Committee of Karol Marcinkowski University of Medical Sciences.

Statistical analysis was performed using SPSS 12.0 for Windows software. Distribution of variables was checked using Shapiro–Wilk test and nonparametric tests, namely Mann–Whitney's *U*-test and Kruskall–Wallis test were used for testing differences between (among) analysed groups as variables' distribution did not meet criteria for normal distribution. A p value <0.05 was considered statistically significant. Results are expressed as median (range) unless otherwise stated.

3. Results

Our study group consisted predominantly of young, nonobese pregnant women who developed diabetes before age of 20

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