Regulatory Effect of Endothelial Dysfunction and Microcirculation Pathology in Pregnant Women Diagnosed with Diabetes Mellitus

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Abstract

The steady incidence of pregnant women diagnosed with diabetes mellitus in the world stimulates the development of research in this direction and deserve special attention. This article presents new methods in usage factors of endothelial dysfunction in development complications of pregnancy with diabetes mellitus. Aim of this research was to study role of endothelial factors in development of obstetrical and perinatal pathology in pregnant women diagnosed with diabetes mellitus. This paper presents the results of the study of 120 pregnant women diagnosed with diabetes mellitus. They were grouped according to the pregnancy complications (pre-eclampsia) and fetal disorders (moderate and severe asphyxia). The researchers defined blood content of prostaglandins E₂ and F₂α, prostacyclin, thromboxane, endotheline-1, nitrogen oxide and L-arginine. It was established that the decreased concentration of prostaglandins, nitrogen oxide and L-arginine combined with considerable increase of the thromboxane and endothelin in the recent pregnancy period is an unfavorable prognostic factor for the subsequent pregnancy development course and pregnancy outcome. The decreased concentration of prostaglandins, NO and L-arginine combined with considerable increase of thromboxane and endothelin content in early pregnancy period is an unfavorable prognostic factor of the pregnancy development and outcome. The administration of therapy aimed at correction of the endothelial dysfunction is pathogenetically grounded, and its timely administration will provide for the decrease of incidence of pregnancy disorders and obstetrical pathologies in diabetic pregnant women.

Keywords: Pregnancy, Diabetes Mellitus, Endothelial Dysfunction, Obstetrical Pathology, Microcirculation, Diabetic Fetopathy.

Introduction

Diabetes mellitus is one of the most dangerous extra genital diseases for pregnant women that may affect particularly unfavorably pregnancy development course and outcome. Although results of numerous studies conducted on diabetes mellitus and its effect on pregnancy, the incidence of the pregnancy complications associated with it remains high, up to 80%. These complications are characterized with severe clinical patterns and are difficult to be cured [1-3]. High incidence of pregnancy and labor complications, disordered feta land newborn development (diabetic footpath, fetal infections, respiratory dysfunction, etc) [4-5] combined with mother’s diagnosis of diabetes mellitus stipulate for high perinatal mortality figures, which range from 70 to 300%, according to various authors [2-3]. Today the pathological mechanisms of pregnancy complications and perinatal pathology development remain unrecognized, particularly, the endothelial dysfunction effect, which hasn’t been didn’t sufficiently studied yet. According to the up-to-date data, nitrogen oxide (NO), L-arginine, prostaglandins E₂ (PgE₂) and F₂α (PgF₂α), prostacycline (PgI₂) and endothelin-1 (Et-1)
are considered to be the most potent vasoactive factors which are produced by the vascular endothelial cells. Apart from this, thromboxane (TxB2) is formed in thrombocytes and acts as an antagonist of Pgl2 [6-7]. The studies proved that NO and Et-1 act as unique mediators of the intracellular interaction, which support the body's homeostatic parameters by maintaining basal vascular tone due to mutual coordination; improvement of rheological blood properties by coordinating blood units aggregation; setting the vascular wall permeability, providing for the "physiological rest" of the uterus. The only source of NO in the human body is the amino acid L-arginine [8-10].

The coordinated process of interaction of these substances provides for the best microvascular tone [8, 11]. Mordwinkin et al. made the research to demonstrate that levels of endothelial progenitor cells in maternal serum are decreased. Also in the peripheral blood of women with gestational diabetes mellitus was evaluated decreased expression of superoxide dismutase and increased endothelial nitric oxide synthase. These findings shows that hyperglycaemia leads to increased oxidative stress and endothelial dysfunction.[12]. Lappas et al. found increased expression of angiogenic proteins and adhesion molecules in omental adipose tissue from women with gestational diabetes mellitus and pre-existing obesity at Caesarean section. [13].

The authors analyzed modern medical literature and considered the increasing interest in the clinical and experimental trials dedicated to the importance of these factors for the vascular pathology development, although the amount of publications on cases of patients with diabetes is quite limited. Therefore, the aim of the study was to research the endothelial dysfunction and its relation to obstetrical pathologies in diabetic women. Aim of this research was to study role of endothelial factors in development of obstetrical and perinatal pathology in pregnant women diagnosed with diabetes mellitus

Methods and Materials

In order to reach the aim mentioned above the authors detected blood content of prostaglandins E2 and F2α, prostacycline, thromboxane, endothelin-1, NO and L-arginine in 120 pregnant women with diabetes mellitus, according to the present pregnancy complications (pre-eclampsia) and fetal disorders (moderate and severe complications). An enzyme immuno detection method was used for estimation blood content of prostaglandins. The radio immuno detection of prostaglandin E2 was performed using the treating compound sets of the «clinical Assay » or «Seragen» companies (the USA), prostaglandin F2α-commercial sets of The Institute of Nuclear Research (Hungary).Due to the fact that prostacyclin (Pgl2) and thromboxane B2 are very unstable compounds, which may quickly transform into more stable ones - 6-keto-PgE1a and thromboxane B3, it was decided to study the content of the latter compounds. The content was detected using the enzyme immunodetection method with the treating compound sets of the «Amarsham Pharmacia Biotech» company (Great Britain).

The endothelin-1 blood content was detected by means of the enzyme immunodetection method with the treating compound sets Endothelin-1 ELISA system (code RPN 228) of the «Amarsham Pharmacia Biotech» company (Great Britain). The preliminary extraction of the Et-1 was performed using the micro columnsAmperC18, 100 mg (code RPN 228), oligopeptide was eluted by the 60% solution of acetonitrile in the 1% solution of trifluoroacetate.

To provide for the effective extraction, control sample of Et-1 with the mentioned concentration was extracted simultaneously with the analyzed samples. The NO content was detected by the content of nitrates and nitrites using the Gris method. The blood content of L-arginine was analyzed using the photometric method.

Results and Discussion

The only verification of the basic vascular components’ parametric alterations in diabetic patients during pregnancy, including the moderate and possibly hazardous ones, doesn’t prove neither their effect on the pregnancy and lab our complications nor disorders of the fetus and newborns. In order to study the relation between prostaglandins and endothelial factors and the pregnancy complications and perinatal pathology incidence, these special characteristics has been analyzed. The obtained results are presented in tables 1 and 2.
It is particularly important that the data in table 1 were obtained from the women in their early pregnancy, before the recalled complications had developed. Opposite to this, when the study was performed in the late pregnancy period, most of the complications manifested clinically. So, tables 1 and 2 are considerably different as the figures in the first table are the evidence of the prognostic importance of the parameters, while the figures in the second one provide for detection of their pathogenetical and path physiological effect. Hereafter the results of the table are analyzed. Pre-eclampsia is a common complication peculiar for the diabetic pregnant women, which may profoundly affect its outcome [14].

Early pregnancy of the women with late pre-eclampsia, is characterized with elevated levels of TxB2 and Et-1, and the blood content of prostacyclin, NO and L-arginine is lower than that in patients without complicated pregnancy. If during the early pregnancy content of TxB2 and Et-1 is increased, and content of prostacyclin, NO and L-arginine is decreased, pre-eclampsia is twice more likely to occur here than in women with compensated equilibrium of the characteristics. Grave imbalance of the endothelial system which appeared in the early pregnancy will alter prostaglandin system in the late pregnancy period. This is quite essential as the high content levels of PgF2α, TxB2 and Et-1 is the evidence of the increased arterial tone, which results from the neurohumoral regulation imbalance with vasoconstriction factors prevailing. Such imbalance may lead to the pre-eclampsia development, which was demonstrated by the studies [1-17].

The parameters of prostaglandins in early pregnancy period don’t show the statistically important relation to the pre-eclampsia development. During the late pregnancy period, when pre-eclampsia is already clinically manifested, all basic clinical characteristics are very important. The particularly important characteristics are decrease of prostacyclin and NO content: pre-eclampsia diagnosed in 85.3% of women with the NO content lower than 3,5 pg/mole and PgF2α lower than 86.4 pg/ml. In case of increased content of the Et-1, which exceeded 8.2 pg/ml and TxB2 more than 40.5 pg/ml, Pre-eclampsia was diagnosed just in 90.5% of the pregnant women. So, it is worth adding to the well-recognized controlled quantity characteristics (arterial pressure, arterial pressure,

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**Table 1:** Blood content of prostaglandins and endothelial factors in women during their early pregnancy, considering the pregnancy complications and perinatal pathologies

<table>
<thead>
<tr>
<th>№</th>
<th>Groups of pregnant women diagnosed with diabetes</th>
<th>PgEα ng/ml</th>
<th>PgF2α ng/ml</th>
<th>Pgl α pg/ml</th>
<th>TxB2 pg/ml</th>
<th>Et-1 pg/ml</th>
<th>NO _VLAN 1/mole</th>
<th>L-arginine, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Without pregnancy complications</td>
<td>2.63±0.14</td>
<td>0.91±0.11</td>
<td>44.1±2.5</td>
<td>60.3±8.2</td>
<td>14.1±1.4</td>
<td>2.09±0.11</td>
<td>38.6±1.2</td>
</tr>
<tr>
<td>2.</td>
<td>Pre-eclampsia</td>
<td>1.79±0.07</td>
<td>0.78±0.09</td>
<td>32.8±3.2</td>
<td>82.7±7.3</td>
<td>17.9±1.6</td>
<td>1.82±0.04</td>
<td>30.0±1.1</td>
</tr>
<tr>
<td>3.</td>
<td>Moderate and severe asphyxia of the newborns</td>
<td>2.71±0.22</td>
<td>1.09±0.05</td>
<td>30.4±2.6</td>
<td>82.1±1.5</td>
<td>18.2±1.5</td>
<td>1.90±0.07</td>
<td>32.5±1.1</td>
</tr>
</tbody>
</table>

**Table 2:** Blood content of prostaglandins and endothelial factors in women during their late pregnancy, considering the pregnancy complications and perinatal pathologies

<table>
<thead>
<tr>
<th>№</th>
<th>Groups of pregnant women diagnosed with diabetes</th>
<th>PgEα ng/ml</th>
<th>PgF2α ng/ml</th>
<th>Pgl α pg/ml</th>
<th>TxB2 pg/ml</th>
<th>Et-1 pg/ml</th>
<th>NO _VLAN 1/mole</th>
<th>L-arginine, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Without pregnancy complications</td>
<td>2.5±0.07</td>
<td>0.64±0.05</td>
<td>79.8±8.1</td>
<td>60.3±8.2</td>
<td>14.6±1.7</td>
<td>2.10±0.09</td>
<td>41.2±1.4</td>
</tr>
<tr>
<td>2.</td>
<td>Pre-eclampsia</td>
<td>1.60±0.10</td>
<td>0.88±0.08</td>
<td>32.8±4.3</td>
<td>96.2±9.8</td>
<td>18.5±1.5</td>
<td>1.68±0.07</td>
<td>36.6±1.2</td>
</tr>
<tr>
<td>3.</td>
<td>Moderate and severe asphyxia of the newborns</td>
<td>2.61±0.22</td>
<td>1.39±0.05</td>
<td>43.7±2.7</td>
<td>91.7±3.4</td>
<td>22.7±1.4</td>
<td>1.86±0.08</td>
<td>33.7±1.2</td>
</tr>
</tbody>
</table>

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proteinuria, etc.) four parameters more: content of prostacycline, thromboxane, Et-1 and NO. Asphyxia of the newborns, which, according to our data, was established in more than a half of all examined pregnant diabetic women, is mostly defined by the microcirculation in the uterus-placental complex and the intensity of the uterus-placental blood circulation. The latter is provided by the regular action of the vascular tone mediators and endogenous prostaglandins. From the other point of view, many researchers note increased synthesis of nitrogen oxide in the females during the pregnancy [16, 18,19].

The capacity of NO to participate in maintaining the microcirculation flow basal vascular tone by vascular relaxation, which leads to the decrease of the general peripheral vascular resistance and increase of the volume circulation, becomes especially important while dealing with the additional (placental) blood circulation circuit, the adequate developmental conditions of the fetus to be provided. Nitrogen oxide is also a regulating agent of the vascular permeability, providing for the rheological blood properties regulation [1, 20, 21].

The vascular mediators which exert opposite effect onto the vascular tone and resistance disrupt placental microcirculation processes and cause chronic oxygen deficiency of the fetus which may lead to severe abnormalities in the fetus and newborn [18]. The metabolic and neuro-endocrine alterations in diabetes, according to the feedback principle, may cause microcirculation disorders accompanied with impaired transporting of oxygen through the placenta and the subsequent development of the placental insufficiency. The relation of the fetal hypoxia in diabetic pregnant women to the essential figures is already observed in the early pregnancy period (see table 1). It is evident that the decrease of the prostaglandins, NO and L-arginine content, of the blood aggregation properties as well as the vascular resistance, lead to aggravated uterus-placental perfusion due to high content levels of Et-1 and thromboxane. These factors may directly cause hypoxia in the fetus and asphyxiation in the newborn.

**Conclusion**

In this paper, for the first time, was made an attempt to create a group of a high risk among women diagnosed with diabetes mellitus. This study provides method for screening evaluation of the endothelial factors before appearance of the clinical manifestations. Obtained results serve to create a group of an increased risk for obstetrical and perinatal complications development. So, the revealed endothelial dysfunction in diabetic pregnant women may be a link in the chain of pre-eclampsia and perinatal complications development.

The decreased concentration of prostaglandins, NO and L-arginine combined with considerable increase of thromboxane and endothelin content in early pregnancy period is an unfavorable prognostic factor of the pregnancy development and outcome. The administration of therapy aimed at correction of the endothelial dysfunction is path genetically grounded, and its timely administration will provide for the decrease of incidence of pregnancy disorders and obstetrical pathologies in diabetic pregnant women.

**References**


