7 SUMMARY

This work deals with the role of adipose tissue-derived hormones – adipokines in the development of insulin resistance in pregnant women with gestational diabetes mellitus (GDM). The study consists of two parts. In the first one, the characterization of changes in concentrations of circulating adiponectin – the most abundant adipokine – during menstrual cycle in healthy women was performed. The second part was focused on the changes of gene expression in pregnant women with GDM relative to healthy pregnant controls (14 vs. 13 subjects). Specificial attention was focused on adipokines and their receptors (ADIPOQ, ADIPOR1, ADIPOR2, LEP, RETN, TNFα, CFD a PAI1) as well as other genes potentially contributing to the etiopathogenesis of GDM in the samples of placenta, subcutaneous, and visceral adipose tissues obtained during surgical delivery.

The changes of gene expression were assessed by the two approaches: Firstly, the gene expression of insulin signaling pathway regulators was characterized using expression arrays in a limited subset of samples from GDM and control subjects. Secondly, the expression of genes that differed most significantly in GDM vs. control group in arrays, together with other genes of involved in the regulation of insulin sensitivity, were analyzed using qPCR in the entire study population. The results of gene expression changes were correlated with the concentrations of relevant circulating parameters (adiponectin, leptin, resistin, insulin, C-peptide, glucose, glycosylated hemoglobin, IGF1, IGFBP1, triglycerides, prolactin, and estradiol) measured in peripheral maternal and umbilical blood collected during delivery.

We conclude that changes in sex hormones during the menstrual cycle do not affect total circulating adiponectin levels in healthy women. Therefore, the differences in insulin sensitivity in various phases of the menstrual cycle are not due to changes of circulating adiponectin levels.

Using the insulin signaling pathway-focused arrays we have characterized 26 out of 112 analyzed genes with significantly changed gene expression in at least one of analyzed tissues of GDM patients compared to healthy controls. Besides the genes involved in postreceptor insulin signaling (Ras-Raf a MAP-kinases pathway), the differently expressed genes were analyzed by qPCR in cohorts of GDM and control pregnant women. Statistically significant differences in gene expression were found in 17 out of 27 qPCR-analyzed genes (Table 28).

Significant elevations of insulin, triglycerides, prolactin, and estradiol serum concentration and decrease in serum concentration of adiponectin were detected in all pregnant women comparing to non-pregnant controls. Serum concentrations of leptin, resistin, glucose and glycosylated hemoglobin were significantly higher in patients with GDM relative to healthy pregnant women.

In the most of genes described in Table 1 the significant relevancy to insulin-resistance status development has been discussed rather sporadically and without cross-regulations. Therefore it seems to be necessary to focuse on them in future studies.

The results indicate that visceral and subcutaneous adipose tissues play different roles in the pathogenesis of GDM. Moreover, the differences in expression pattern of syncytiotrophoblast reflect alterations in GDM patients, as well.

Although further studies are needed to fully characterize the contribution of respective gene expression changes to GDM development the results of our work may serve as an important and innovative background for further studies of GDM and its pathogenetic proximity to type 2 DM and/or obesity.