Diabetes mellitus in pregnancy activates the innate immune response on neonatal monocyte

Sakika Yanai, Daisuke Tokuhara[2)]*, Daisuke Tachibana[1)], Mika Saito[2)], Haruo Shintaku[2)], Masayasu Koyama[1)]

1) Department of Obstetrics and Gynecology and 2) Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka,Japan.

Introduction

- Diabetes mellitus (DM) in pregnancy causes congenital malformation, macrosomia, respiratory distress syndrome, and other abnormalities in neonates.
- And, these offspring have a high risk of developing obesity, impaired glucose tolerance, and type2 DM in adulthood.
- It has been proposed hypothesis that DM is caused by activated innate immunity, but whether maternal DM affects the neonatal innate immune system is unknown.
- We aimed to reveal the influence of DM in pregnancy on the toll-like receptor (TLR)–mediated innate immune response in neonates.

Materials and Methods

- Cord blood was collected after full-term vaginal or cesarean delivery and classified into a DM group (n = 8) and non-DM (control) group (n = 7).
- Mononuclear cells were harvested from cord blood by using density gradient centrifugation, after which anti-CD14 magnetic beads were used to isolate monocytes from the mononuclear population.
- After monocytes were cultured with lipopolysaccharide (LPS;TLR4 ligand), flagellin (TLR5 ligand), Pam3CSK4 (TLR1/TLR2 ligand), zymosan (TLR2/TLR6 ligand), or macrophage-activating lipopeptide (MALP;TLR2/TLR6 ligand) for 12 h, the cytokine levels (interleukin [IL]-8, IL-6, IL-1β, IL-10, tumor necrosis factor alpha and IL-12) in the culture supernatants were measured.

Results

	DM group(n=8) GDM=5, overt DM=2,type2DM=1	control group(n=7)	P value*
age (yr)	35±5	33±6	NS
BMI	26±3	19±1	p<0.00
Gestational weeks at delivery(wks)	38±2	38±2	NS
Mode of delivery	CS=3,VD=4	CS=4,VD=4	NS
Blood glucose**(mg/dl)	126±42	112±32	NS
HbA1c(NGSP)(%)	6.1±1.1	5.4±0.2	NS
Treatment	Insulin=6,diet=1		

Table 1. Clinical characteristics of mothers

	DM group(n=8)	control group(n=7)	P value*
Birthweight(g)	2993±572	3194±339	NS
Apgar score(5min)	9±0.5	9±0.4	NS
Umbilical artery pH	7.320±0.02	7.317±0.05	NS
Umbilical artery PO2 (mmHg)	19.1±5.7	23.9±11.0	NS
Umbilical artery PCO2 (mmHg)	45.7±2.9	42.1±6.5	NS
IgM in cord blood(mg/dl)	8.1±1.8	9.3±1.8	NS
Blood glucose in cord blood (mg)	66±22	68±29	NS
Insulin in cord blood(μIU/ml)	5.47±3.56	2.44±0.90	NS

Table 2. Clinical characteristics of neonates

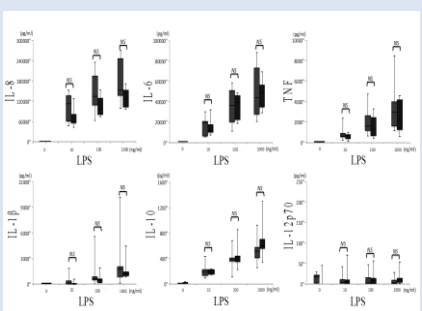

Figure 1. Cytokine profiles after LPS stimulation

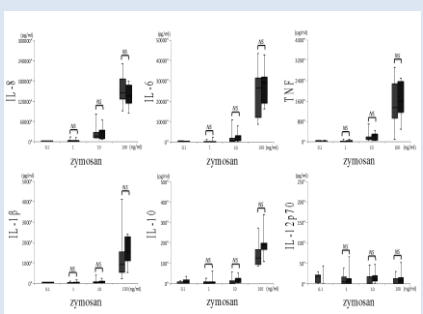

Figure 2. Cytokine profiles after zymosan stimulation

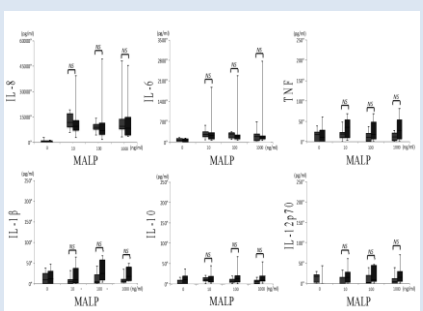

Figure 3. Cytokine profiles after MALP stimulation

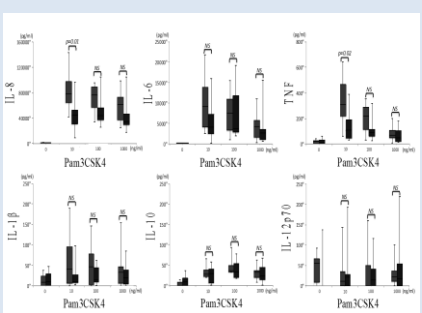

Figure 4. Cytokine profiles after Pam3CSK4 stimulation

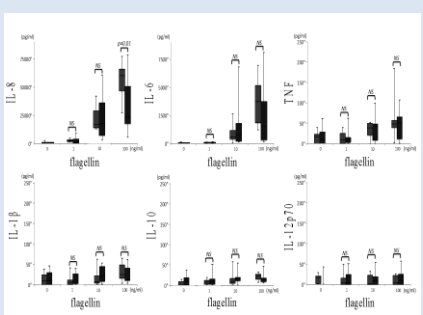

Figure 5. Cytokine profiles after flagellin stimulation

- Compared with the control group, the DM group had higher concentrations of IL-8 (*P*=0.01) and tumor necrosis factor alpha (*P*=0.02) after monocyte cultures were stimulated with Pam3CSK4 and higher concentrations of IL-8 (*P*=0.01) after flagellin treatment.
- In contrast, stimulation with lipopolysaccharide, zymosan, or macrophage-activating lipopeptide did not lead to any difference in cytokine profiles between the two groups.

Disucussion

- Diabetes mellitus is caused by activated innate immunity.
- The plasma concentration of inflammatory mediators is increased in the insulin-resistant stated of obesity and type2 DM.
- Inflammation modulate insulin resistance in GDM.
- Offspring of women with GDM have a high risk of developing obesity and type2 DM in adulthood.

Fernandez-Real, et al., 2012; Pickup, et al., 1997; Ategbo, et al., 2006; Akadiri, et al., 2011

- DM in pregnancy induces a hyper activation of TLR5 or TLR1/2-mediated signaling in neonates.

DM in pregnancy induce a high risk of DM and obesity to neonates in adulthood through activating TLR5 or TLR1/2-mediated signaling.

Conclusions

Diabetes mellitus in pregnancy induces excessive inflammatory activation in neonates via a TLR5- or TLR1/2-mediated innate immune response.