



Abstracts of JPA meeting 2019

1.

A CASE OF EXTRA-ABDOMINAL UMBILICAL VEIN VARIX WITH SEVERE FETAL ANEMIA

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Introduction: Umbilical vein varix (UVV) is rare vascular anomaly associated with a high incidence of fetal demise and fetal growth restriction. We present a case of extra-abdominal UVV with severe anemia diagnosed by Doppler ultrasound antenatally. We also reviewed relevant literatures of extra-abdominal UVV.

Case: A 33-year-old primigravida was referred to our hospital for fetal growth restriction, fetal cardiomegaly and decreased fetal movements at 26 weeks' gestation. Doppler assessment showed an elevated middle cerebral artery peak systolic velocity (MCA-PSV) at 2.2 MoM, suggesting fetal anemia. Cordocentesis revealed hemoglobin at 1.9 g/dL and hematocrit at 6.9%. Consequently, red blood cells were transfused to the fetus. MCA-PSV decreased to 1.1 MoM instantaneously, and fetal hydrops disappeared 7 days later. Ultrasound examination revealed marked turbulent flow through a 13 mm diameter dilatation of the fetal extra-abdominal UVV. At 33 weeks' gestation, the patient underwent cesarean delivery due to nonreassuring fetal status, and a 1,334g (1st percentile) female was born, with Apgar scores of 4 at 1 min and 7 at 5 min. Pathological analysis revealed focal vascular smooth muscle tear of the umbilical vein. Epileptic encephalopathy and cerebral palsy with delayed myelination were diagnosed. Permanent tracheotomy was performed due to respiratory failure at 7 months of age.

Conclusion: Extra-abdominal UVV can present as fetal hydrops with anemia. In the ultrasound examination of fetal anemia, umbilical cord screening should be performed cautiously.

2.

THE FETAL/PLACENTAL WEIGHT RATIO IS ASSOCIATED WITH THE INCIDENCE OF ATOPIC DERMATITIS IN FEMALE INFANTS DURING THE FIRST 14 MONTHS: THE HAMAMATSU BIRTH COHORT FOR MOTHERS AND CHILDREN (HBC STUDY)

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Introduction: The present study aimed to investigate the relationship between the fetal/placental weight ratio and incidence of atopic dermatitis during the first 17 months.

Methods: Study participants were 922 infants from singleton pregnancies enrolled in the Hamamatsu Birth Cohort for Mothers and Children (HBC Study) after excluding 298 subjects for missing data on atopic dermatitis. The enrollment of atopic dermatitis was based on a positive response from

parents regarding whether a physician had ever diagnosed their child with atopic dermatitis by 17 months of age.

Results: Maternal and perinatal factors did not correlate with the incidence of infantile atopic dermatitis. The fetal/placental weight ratio, but not birth or placental weight, correlated with the incidence of atopic dermatitis in female, but not male, infants. A correlation was still observed after adjustments for maternal allergy, gestational age at birth, maternal smoking during pregnancy, and household income at birth (OR: 1.57, 95% CI: 1.05-2.33).

Discussion: We speculated that the balance between fetal and placental growth may represent, at least partly, a specific history of exposure to unidentified environmental insults, including that which presumably programs a predisposition in female infants to atopic dermatitis.

3.

NICOTINE TRANSPORT AND SUPPRESSIVE EFFECT ON NUTRIENT TRANSPORT SYSTEM IN BEWO CELLS

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Objective: Maternal nicotine exposure via smoking has been associated with birth complications, such as fetal growth restriction. However, the mechanism underlying the transplacental transfer of nicotine and its influence on nutrient transport system have been unclear. In this study, we investigated the mechanism of nicotine uptake and the influence of nicotine on the glucose and amino acid transport system, using BeWo cells as a model of the human placental trophoblast.

Methods: BeWo cells were incubated with [³H]nicotine and used for the uptake study. Furthermore, BeWo cells were incubated with [³H]3-O-methyl-D-glucose (3-OMG) or [³H]aminoisobutyric acid (AIB), and the effect of nicotine on the uptake of both compounds was examined. The amount taken up by the cells was measured by liquid scintillation counting.

Results: [³H]Nicotine uptake was time-, temperature- and pH-dependent and showed saturation kinetics with a Michaelis constant Km of 300.6 μM. In addition, the Eadie-Hofstee plots were linear, suggesting that a single transport system was involved in nicotine uptake in BeWo cells.

Nicotine and its metabolite cotinine showed concentration-dependent inhibitory effects on [³H]3-OMG uptake. In the presence of nicotine, a Michaelis Vmax of 3-OMG significantly decreased. On the other hand, [³H]AIB transport was not suppressed by nicotine.

Conclusion: These results suggest that a specific transport system is involved in the uptake of nicotine in BeWo cells, and the nutrient supply to fetus may be affected by nicotine exposure.

4.

CONSERVATIVE TREATMENT OF RETAINED PRODUCTS OF CONCEPTION AFTER ABORTION OR DELIVERY IN 33 PATIENTS

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Objective: Retained products of conception (RPOC) is associated with postpartum hemorrhage and intrauterine infection. Although critical obstetric hemorrhages occur in some cases, conservative treatment was possible in recently reported cases. Against this background, we conducted this retrospective study for cases of RPOC treated at our hospital.

Methods: Consecutive 33 cases who were diagnosed with RPOC between 2000 and 2018 were retrospectively analyzed. The major axis of the remaining tissue was measured on ultrasound and/or MRI images taken at the time of diagnosis, and compared. After that, S-hCG levels were observed from 22 cases, and their outcome was evaluated.

Results: 8 cases were classified as Group A, who required blood transfusion before hemostasis was achieved soon after delivery of the baby. 4 cases belonged to Group B, who experienced massive hemorrhage, and required blood transfusion during the period of conservative treatment. Group C is comprised of the other 21 cases, who experienced no major trouble throughout the period of conservative management. The retained placenta of Group A was bigger than group C, although there was no significant difference between group A and B. During the conservative treatment, the levels of S-hCG gradually decreased with the half-life of approximately five days, disappeared rapidly after hemostatic therapy or removal of the retained placenta. Importantly, no patient needs hysterectomy.

Conclusion: RPOC cases who require hysterectomy seem to be very rare, although some patients experience massive hemorrhage.

5. IN VIVO IMAGING TO VISUALIZE FETO-MATERNAL INTERFACE IN PREGNANCY-ASSOCIATED HYPERTENSION MOUSE

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Object: Hypertensive disorders of pregnancy (HDP) is thought that placental dysfunction is important in the pathogenesis. The morphological change is important, but it has not been well documented the fetoplacental vasculature. I try to reveal the detail of vascular system to understand HDP, and I decide to use the in vivo imaging (two-photon microscopy) technology and emerging tissue-clearing technologies (the Scale system).

Methods: As the model of HDP, we generated a transgenic mouse model that developed pregnancy-associated hypertension (PAH) by the overproduction of Ang II in maternal circulation during late pregnancy. To figure out vascular formation, I used three-dimensional (3D) observation of whole tissues and tissue-clearing technology, the Scale system. I prepare for R26GRR mice that is a ROSA26 knock-in Cre-reporter exhibiting green emission before and red after Cre-mediated recombination. Then I combined R26GRR mice and Tie2-Cre-PAH mice (Tie2 gene is vascular endothelial cell-specific expression.). Then I combine placenta of R26GRR/Tie2-Cre/PAH mice together with the microscopy to form 3D imaging.

Result: I established the method for visualizing placental vessels with fluorescence. It revealed that the vascular networks of PAH mice were rough than WT mice by two-photon microscopy.

Conclusion: I successfully observed feto-maternal interface using tissue-clearing agent and in vivo 3D imaging. This technique will contribute that to elucidate the feto-maternal interface with normal pregnancy and HDP including effects of anti-hypertensive drugs.

6. LNCRNA 1600012P17RIK IS A MOUSE PLACENTA-SPECIFIC LNCRNA

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Objective: Long non-coding RNAs (lncRNAs) exert functions in regulating various biological processes. However, there is little information available on the expression and function of mouse placenta-derived lncRNAs. The purpose of this study was to identify mouse placenta-specific lncRNAs.

Methods: For in silico lncRNA expression pattern analysis, we analyzed the lncRNA expression profile in E10 and E17 mouse placenta using the FANTOM5 database. For in vivo lncRNA expression analysis, we performed real-time PCR to examine whether selected lncRNAs were associated with the placenta using B6D2F1 mouse placentae at different stages (from E7.5 to E18.5) and adult organs.

Results: In silico analysis revealed that approximately 350 lncRNAs were expressed in both E10 and E17 mouse placentae. In the 10 most highly expressed lncRNAs in these placentae, we found 2 mouse placenta-specific lncRNA candidates that were exclusively or predominantly expressed in the placenta compared with adult organs. Among these candidates, we selected 1600012P17Rik lncRNA that was the highest expression lncRNA in E17 placenta (55%). In vivo real-time PCR analysis showed that 1600012P17Rik was expressed exclusively in the mouse placenta but not in any other organs used in this study. During placenta development, 1600012P17Rik was hardly detectable at E7.5 and began to increase thereafter, reaching peak expression at E16.5.

Conclusion: lncRNA 1600012P17Rik was a mouse placenta-specific lncRNA and was expressed in a developmental stage-specific manner.

7. GLUCOCORTICOID WEAKENS FETAL MEMBRANES VIA IL-1B PRODUCTION BY AMNIOTIC FLUID MACROPHAGE

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Objectives: Glucocorticoid (GC) use during pregnancy is known to increase the risk of preterm birth and preterm premature rupture of membranes (pPROM). Here, we investigated the mechanism of how GC weaken the fetal membranes (FM).

Methods: The thickness of FM between control pregnant women and patients treated with GC was measured. Corticosterone (C) was subcutaneously injected to pregnant mice daily from 12 to 18 dpc. FM were collected and used for immunofluorescence and quantitative RT-PCR. The thickness of FM was measured. Primary human amnion mesenchymal cells (hAMC) were incubated with hydrocortisone (HC) or IL-1B for 24 or 48 hours.

Results: The amnion mesenchymal layer was significantly thinner in GC treated pregnant patients and in C-injected mice than in control groups. *COL1A1* mRNA was decreased and *COX2* mRNA and *PGE2* synthesis were increased by C. Proliferation and migration of macrophages (M) were observed around C-injected amnion. In immunofluorescence, IL-1B was localized to these migrated M. In hAMC, HC did not change *MMP* and *COX2* mRNA expressions, but treatment of IL-1B significantly increased *MMP* and *COX2* mRNA levels. Furthermore *COL1A1* mRNA levels was decreased by both HC and IL-1B.

Conclusion: GC weakens amnion via collagen degradation by MMP and suppression of collagen synthesis. Induction of MMP and prostaglandin synthesis would be mediated by IL-1B from recruited amniotic fluid M, and both released IL-1B and GC decrease transcription of collagen genes. Collectively, these results indicated that GC plays a pivotal role in the pathogenesis of pPROM.

8. ANALYSIS OF UTERINE DCS BEFORE IMPLANTATION

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