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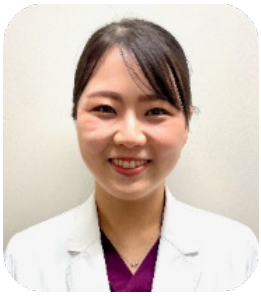
(Y1)



A nationwide survey and feasibility study of virtual telehealth visits for perinatal checkups during the COVID-19 pandemic in Japan

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Objective: To explore the recent use of virtual telehealth visits (VV) for perinatal checkups in Japan during the COVID-19 pandemic, define problems related to its use, and to examine the feasibility of VV use hereafter.

Methods: (1) Questionnaire surveys with birthing facilities throughout Japan (January 2021) (2) Questionnaire surveys among pregnant and parturient women attending Osaka and Keio University hospitals (May - July 2021). (3) Comparative study to determine the future feasibility of VV between the women's self- and healthcare provider' s- measurements of blood pressure (BP), fundal height (FH), urine test and fetal heart rates (FHR) (May - July 2021).

Results: (1) Survey responses were received from 1,096/2,214 (49.5%) of all birthing facilities. Only 1.6% of the birthing facilities had already introduced VV, primarily due to healthcare providers not perceiving maternal demands for it. (2) 96 women participated in the surveys. 60.2% of them were anxious about in-person visits, and 36.6% favored the introduction of VV. (3) The Pearson's correlation coefficients between the women's self- and healthcare provider' s- measurements for systolic and diastolic BP and FH were 0.68, 0.58 and 0.87; concordance rates for proteinuria and urinary glucose test were 91.6% and 98.9%, respectively, indicating good feasibility for VV. In contrast, there was poor correlation for fetal heart rate (-0.04) and Bland-Altman analysis revealed 95% limits of agreement ranging from -42.6 to 65.6 bpm, indicating the need for method improvement. Surveys of difficulties encountered in self-measurement indicated that more patients had difficulty with the FH and FHR than with BP and urine test.

Conclusion: In Japan, the introduction of VV for perinatal checkups during the COVID-19 pandemic was limited, mainly due to a failure by healthcare providers to recognize the desires of pregnant and parturient women for VV. VV with some modifications will be feasible for perinatal checkups, which should encourage proactive discussions about VV perinatal checkups for the new era.

Chih-Wei Lin 林智偉
(Y2)

Clinical outcomes of nirmatrelvir-ritonavir use in pregnant women during the Omicron wave of the coronavirus disease 2019 pandemic

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Objectives: to report the use of paxlovid in pregnant women with COVID-19.

Materials and Methods: Pregnant women attending a tertiary referral hospital in Taiwan from 29 April to 30 July 2022 were enrolled in the study. We compared baseline characteristics, clinical manifestations, and adverse events between paxlovid-treated women and those without paxlovid use. Maternal and neonatal outcomes were analysed in women who delivered during the study period.

Result: A total of 30 paxlovid-treated pregnant women and 55 women without paxlovid use were included in the analysis. The mean duration of COVID-19-associated symptoms in the paxlovid-treated women was shorter than that in the control group (10.10 days versus 15.59 days, p = 0.04). No severe adverse events due to paxlovid use were observed. Dysgeusia and diarrhoea were the most common adverse effects. Thirteen paxlovid-treated and 28 untreated women delivered during the study period. More pregnant women in the paxlovid group who delivered during the study period underwent caesarean delivery compared to the group without antiviral treatment (10 of 13 [76.92%] versus 12 of 28 [42.86%], p = 0.042), and insignificantly more newborns were born small for gestational age in the paxlovid group compared to the control group (3 of 13 [23.08%] versus 1 of 28 [3.57%], p = 0.086).

Conclusion: Our study showed that paxlovid was effective and safe for pregnant women during the Omicron wave of the COVID-19 pandemic. A higher proportion of caesarean delivery rates was observed among paxlovid-treated women. Long-term follow-up of pregnant women exposed to paxlovid and their offspring is needed.

Da Hyun Wang
(Y3)

15 year's experiences of External Cephalic Version Clinic in Korea

Background: The continuous increased in the rates of cesarean section worldwide is concerning. Breech presentation is one of the major indications for cesarean section. External cephalic version (ECV) can reduce cesarean rates by approximately two-thirds in term breech pregnancies.

We have been running the largest ECV clinic in South Korea since 2008, and from 2015, ECV trials were started at outpatient clinic. This study aims to verify the safety of ECV, and to share experiences of running the ECV clinic by managing more than 2,000 patients over 15 years.

Methods: From August 2008 to December 2023, 2115 term breech pregnant women visited our ECV clinic. Ultrasonography and electric fetal monitoring were checked before the ECV to verify fetal position and fetal well-being. Women with gestational age over 36 weeks were candidates for ECV. Candidates were excluded if there was any contraindication to labor or vaginal birth (such as placenta previa, or previous uterine operation) and to ECV (such as non-assuring fetal monitoring, abruptio placenta, pre-eclampsia, congenital fetal anomalies, significant intrauterine growth restriction, oligohydramnios, previous cesarean section≥2, cord neck≥3, tense abdomen and fetus engaged in the pelvis tightly on physical examination).

From January 2015 to until now, we have started ECV clinic at outpatient department (OPD) basis with two track of ECV trials. All available ECV candidate were first allocated to OPD ECV clinic. After once or twice simple soft trials at the ultrasound room, difficult candidates were allocated to delivery room (DR) and favorable cases were done right on the spot. Candidates whom directly allocated to DR after soft trials and failed candidates of OPD ECV trials were tried at DR after preparation with pre-operation labs and I.V. lines.

We analyzed medical records of ECV trials retrospectively, and then, evaluated the characteristics of ECV patients, outcomes and short term complications.

Results: In total 2115 pregnant women visited our ECV clinic, and among them, 1689 had received ECV trials. From 2015 to 2023, in 1397 cases of ECV trials, 626cases were performed at OPD, 302 cases were performed at DR, and 443cases were first performed at OPD and then tried again at DR. The success rate of ECV is 84.8%(531/626), 52.3%(158/302) and 65.4%(290/443) respectively. Total success rate of ECV (including OPD and DR) is 71.4%(979/1371). Complications of ECV trials were mostly temporal fetal bradycardia (38%) and short periods of decreased fetal heart rate variability were also common(30%); however decreased variability disappeared within 10min in most cases. In addition, few patients had experienced vaginal bleeding (0.005%).

Conclusion: From our experiences, outpatient ECV has a considerable success rate with relatively low complication rates, and can be encouraged.

Min Feng 馮敏
(Y4)

Differential changes of placental soluble epoxide hydrolase (sEH) between normal pregnancies and pregnancies complicated by pre-gestational and gestational diabetes mellitus (GDM)

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Objective: To investigate the role of soluble epoxide hydrolase (sEH) in the inflammatory changes in the placenta in pregnancies complicated by diabetes mellitus (DM) or gestational diabetes mellitus (GDM).

Materials and Methods: Placental samples were analyzed from women with normal pregnancies and those with pregnancies complicated by GDM with and without large-for-gestational-age (LGA) infants and pre-gestational DM. Cytotrophoblast cells (JEG3) were cultured under standard, hyperosmotic control, and hyperglycemic conditions. Streptozotocin (STZ)-induced diabetic pregnant rats were used as an animal model.

Results: In human placental samples, the levels of sEH protein/ mRNA and IL-1β were significantly higher in villous tissues from GDM women with LGA infants and those with pre-gestational DM than in women with normal pregnancies. Women with pre-gestational DM also had higher levels of MCP-1 in the villous tissues than normal pregnant women. In JEG3 cells, hyperglycemic conditions significantly increased sEH protein/ mRNA, IL-1β , and IL-6 levels compared to standard and hyperosmotic conditions. In STZ-induced diabetic pregnant rats, the levels of sEH, phosphorylation of p38 and ERK, COX2, IL-1β , IL-6, and MCP-1 were significantly higher in the placentas compared to normal pregnant rats. Administration of AUDA, a specific sEH inhibitor, significantly reversed these changes induced by STZ. Furthermore, STZ-induced diabetic rats treated with AUDA had significantly higher levels of GDNF but lower levels of VEGF compared to those STZ-treated rats but without AUDA administration.

Conclusion: Our results suggest that sEH participates in the inflammatory changes in the human placenta in pregnancies complicated by DM or GDM and that inhibition of sEH may provide a potential therapy for complications related to diabetes during pregnancy.

Yu-Hao Fan 范祐豪
(Y5)

Predictors of diabetic ketoacidosis and associated perinatal mortality in pregnant women with pregestational diabetes mellitus

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Objective: Diabetic ketoacidosis (DKA) during pregnancy is a life-threatening medical crisis for both mothers and fetuses. The aim of this study was to investigate the predictors of DKA and associated perinatal mortality in pregnant women with pregestational diabetes mellitus (PDM).

Methods: This was a retrospective cohort study of singleton pregnant women with PDM at a tertiary medical center from April 2000 to November 2022. Receiver operating characteristic (ROC) curve analyses were used to evaluate various variables between the mothers with and without DKA, and factors associated with perinatal mortality.

Results: Of the 219 pregnant women with PDM enrolled, 21 were diagnosed with DKA, and 6 (28.6%) fetal deaths were noted. A higher level of HbA1c (8.45 ± 1.92 vs. 6.73 ± 1.01, P = 0.001) and LDL (152.86 ± 55.00 vs. 119.25 ± 36.17, P = 0.012), but a lower level of HDL (38.71 ± 9.84 vs. 57.96 ± 14.47, P < 0.001) were noted in the DKA group than in the non-DKA group. The areas under the ROC curve (AUCs) of HbA1C, LDL, and HDL were 0.79 (95% confidence interval (CI) 0.69-0.89), 0.68 (95% CI 0.53-0.84), and 0.87 (95% CI 0.80-0.94), respectively. Furthermore, a higher level of maternal potassium (5.77 ± 1.17 vs. 4.23 ± 0.55, P = 0.022) and a greater difference of anion gap (22.50 ± 4.46 vs. 15.17 ± 6.48, P = 0.014), but a lower maternal arterial pH (7.07 ± 0.09 vs. 7.20 ± 0.16, P = 0.030) and bicarbonate (3.90 ± 1.67 vs. 9.96 ± 4.48, P = 0.001) were associated with perinatal mortality. The AUCs of maternal potassium, anion gap, pH, and bicarbonate were 0.94 (95% CI 0.84-0.99), 0.87 (95% CI 0.70-0.99), 0.86 (95% CI 0.68-0.99), and 0.93 (95% CI 0.80-0.99), respectively.

Conclusions: HbA1c and lipid profile are valuable predictors of developing DKA in pregnant women with PDM. Severe maternal hyperkalemia and acidosis are associated with perinatal mortality.

Ping-Hsuan Wu 吳品萱
(Y6)

Amniotic fluid stem cell-derived exosomes could show the therapeutic potential in preeclampsia mouse model

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Objective: To investigate the therapeutic potential of amniotic fluid stem cell-derived exosomes (AFSC-exo) in preeclampsia.

Materials and methods: The prevalence of preeclampsia in Taiwan is getting higher and higher over these years. It can cause organ failure with high blood pressure and proteinuria in the mother. It can also cause the fetus to grow retarded in the uterus, premature delivery or even death. We established the preeclampsia model and continuous subcutaneously inject nitric oxide producing enzyme L-NAME starting on the 9th day of pregnancy to induce hypertension and proteinuria in mice. After confirming the induced preeclampsia, the mother mice were injected intravenously with 1*10^10 amniotic fluid stem cell-derived exosomes on the 12th and 14th day of pregnancy.

Results: There are 8 pregnant mice were sacrificed. AFSC-exo were all positive for CD9, CD63 and TSG 101 by Western blot. The morphology studies showed the evidence in nanoparticle tracking analysis and transmission electron microscope. To observe the birth outcome results, lower weight of the fetus, lower weight of the placenta, higher preterm birth rate, and higher maternal mortality were found in the preeclampsia control group. The treatment group improved the destruction of placental endothelial cells and promote blood vessel development proved by placenta and kidney immunohistochemistry studies.

Conclusion: This result could be used in regenerative applications of preeclampsia-related diseases in the future.

Yuya Saito
(Y7)

Use of the Ex-Vivo uterine Environment (EVE) system for Surgery in the Fetal Sheep

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Introduction: Early treatment of fetal congenital or progressive morphological diseases can improve long-term outcomes. Several fetal therapies (FTs) for certain diseases are reported. However, most of them are not radical treatments and always with off-target effects. This study aimed to compare surgical outcomes of fetuses maintained on the EVE system with a standard intrauterine approach.

Methods: Two groups of five animals were randomized to either, an EVE surgery group or an intrauterine (IU) surgery group. In the EVE group, fetal sheep were delivered at 104 days gestation age (GA), connected to the EVE system, and then had open abdominal surgery with a 3 cm wound two days later. Fetuses were then maintained on EVE therapy for 2 days. For the IU group, animals were underwent the same FT as the EVE group at 106d GA, and was remained in utero for a further 2 days. Fetuses in both groups were delivered at 108d GA. Fetal brain, tissues were immunostained with Oligo2, IBF1, and GFAP antibodies for histopathological evaluation of brain white matter injury. Wound healing was assessed with α SMA antibody, and injury healing was compared histopathologically. Hematological markers were used to assess organ injury. Group differences were tested with t-test with $p<0.05$ deemed significant.

Results: All animals completed their protocols. There were no significant differences in fetal sex, birth, or brain weight between the groups. There were significant differences in pH, base excess, lactate and HCO_3^- at 0 hours and pH, base excess, and HCO_3^- between the two groups at 48 hours. Particularly, acidosis was observed at both 0h and 48h in only the IU group. In brain histopathology, there were no significant differences in the number of cells positive for immunostaining with Oligo2, IBA1, and GFAP antibodies in the level of the anterior basal ganglia and mamillary body after euthanasia. In the wound of the skin, α SMA was observed to be expressed in both groups. The wounds were completely dehiscence in 4 animals of the EVE group, and only 1 animal was found to be partially fused. On the other hand, in the IU group, all 5 animals had only partial dehiscence and healing was observed. Wound healing was a better impression in the IU group, however, there was no statistically significant difference in dehiscence between the two groups (p= 0.06).

Conclusion: We report the use of an EVE system to undertake abdominal surgery on preterm fetal sheep at 106d GA. Compared to the IU group, the EVE group appeared to perform better with no acidosis, but wound healing appeared to be delayed. Although a sizable amount of work remains to be done, these data demonstrate the potential utility of an EVE system to facilitate fetal surgical therapy in early gestation pregnancies or where existing approaches are unavailable.

Rie Seyama
(Y8)

The effective method of detecting pathogenic variants for exome negative cases in Cornelia de Lange Syndrome

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Recent studies suggest that transcript isoforms significantly overlap (approximately 60%) between brain tissue and Epstein– Barr virus-transformed lymphoblastoid cell lines (LCLs). Interestingly, 14 cohesin-related genes represented as NIPBL, SMC1A, or SMC3 with variants that cause Cornelia de Lange Syndrome (CdLS) (MIMID#122470), a rare neurodevelopmental disorder with dysmorphic features, are highly expressed in the brain and LCLs. Among 66 CdLS families, we previously performed exome sequencing (ES) and found either pathogenic single nucleotide variants or copy number variants in 46 families (46/66=69.7%), but not in the other 20 families. In this context, we first performed RNA-seq of LCLs from 22 solved (with pathogenic variants) and 19 unsolved (with no confirmed variants) CdLS cases. First, an RNA-seq pipeline was developed using 22 solved CdLS cases and 105 downloaded healthy controls from the Genotype-Tissue Expression (GTEx) Biobank with two different methods: 1) short variant analysis (for single-nucleotide and indel variants) using GATK v4 Broadinstitute pipeline (v.4.0.4.0) and 2) aberrant splicing detection analysis using LeafcutterMD. The efficiency of this pipeline was confirmed using 22 positive control. A total of 19 (86.4%, 19/22) variants among 22 positive controls were confirmed by this RNA-seq. Then, 19 unsolved cases were subsequently applied to our pipeline, and four pathogenic variants in NIPBL (one inframe deletion and three intronic variants) were newly identified. Two of three intronic variants were located at Alu elements in deep-intronic regions, creating cryptic exons. Furthermore, these variants were strongly assumed to change the RNA binding proteins, which affect those splicing events. In summary, by developing the RNA-seq pipeline, four pathogenic variants were newly identified by RNA-seq of 19 CdLS cases that were unsolved using ES analysis. Therefore, the total diagnostic rate increased from 69.7% (46/66) to 75.8% (50/66). The RNA-seq with LCLs was a useful technique in determining hidden variants in ES-negative CdLS cases and is applicable to other Mendelian disorders.

Eun Jin Choi
(Y9)

The impact of maternal hepatitis C virus infection on the congenital malformations

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Objectives: To investigate the effect of maternal hepatitis C virus (HCV) infection on the congenital malformations.

Methods: This nationwide population-based study included women who had singleton pregnancies and delivered birth between 2015 and 2021. The definitions of infection with HCV, as well as congenital malformations, were based on the International Classification of Diseases, 10th revision. To adjust and balance the baseline characteristics, multivariable logistic regression and propensity score matching analyses were performed, respectively, between mothers who were positive for HCV and those who were negative for HCV.

Results: This study included a total of 1,800,057 pregnant women, of whom 1,492 had HCV. Among HCV-positive pregnant women, 200 (13.4%) delivered neonates with congenital malformations. In multivariable analysis, HCV infection was independently associated with an increased risk of congenital malformations of the circulatory system (adjusted odds ratio [aOR], 1.493; 95% confidence interval [CI], 1.180– 1.889; P=0.0008) after adjusting for maternal age, nulliparity, pre-gestational hypertension, pre-gestational diabetes mellitus, and neonatal sex. In PSM analysis, HCV-positive mother (aOR, 1.509; 95% CI, 1.148-1.984; P=0.0032) had a higher risk of neonatal circulatory congenital malformations.

Conclusions: The risk of congenital malformations of the circulatory system was significantly higher in the neonates born to the HCV-positive pregnant women.

Keywords: maternal hepatitis C virus; adverse pregnancy outcomes; congenital malformations

Li-Shan Chen **陳立珊**
(Y10)

Carrier screening for present disease prevalence and recessive genetic disorder in Taiwanese population

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Carrier screening is important to people have a higher prevalence of severe recessive or X-linked genetic conditions. This study is aimed that the frequency and uncertain nature of genetic variants was identified in Taiwanese population, providing individuals with information at risk of inherited diseases and their heritability to newborns. A total of 480 subjects receiving genetic counseling with no family history of inherited disorders were recruited into a cohort from 2018 to 2022. Next-generation sequencing (NGS) panel for autosomal dominant (AD), autosomal recessive (AR) and X-linked diseases was sequenced to assess disease prevalence and carrier frequency for the targeted diseases. Publicly available NGS datasets were analyzed following a tier-based system and ACMG recommendation. 5.3% of subjects showed the presence of variants for genetic disorder, and 2.3% of them were determined with AD. 14 of subjects with pathogenic variants were carriers for AR. The inherited genes were LDLR for AD disorders and AR disorders included GAA and ATP7B. 21.6% of subjects had highest carrier frequency of GJB2 gene. 0.5% of subjects had highest frequency of GJB6 for X-linked condition. In conclusions, the variants in LDLR, GAA and ATP7B genes were identified in Taiwanese population, indicating individuals had higher risk of Pompe disease, Wilson' disease and familial hypercholesterolemia. Taiwanese individuals carrying GJB2 and GJB6 had the considerable risk of hearing loss passing to their offspring.