- 35 cases of twins and triplets, 32.1%

By histological examination,

- Stem villous edema, intermediate villous vessels occlusions, terminal villous avascular, and decidual vascular and other lesions were observed.

By clinical record:

- 21 cases of GDM, 19.2%
- 20 cases of FGR, 18.3%
- 11 cases of HDP, 10.6%

Conclusions: Twins sharing the same ammonium cavity with just one placenta have many complications with VCI.
VCI is a problem on the fatal side, and it can be easily identified by gross examination, as can the problems in the circulation on the mother's side.
VCI shares with HDP the lack of circulation from the mother's side, and clinically, the high rate of complications is due to maternal floor vessels problems.
In regards to GDM, previously the VCI rate was not so high, but recently it has been higher than before. The reason for this is that GDM diagnosis has now become more accurate and can be seen to be more common.
Placental pathology is very effective at explaining clinical states about VCI and my hypotheses regarding the origin of VCI is backed up by both clinical and pathological pictures. These clearly show the link between HDP, GDM, and FGR and lack of circulation on the mother's side and fetal side of the placenta.

69.
AVASCULAR VILLI

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Object: Lack or diminishment of capillaries in the villi of the placenta, known as avascular villi, has several causes. Firstly, there is chromosomal abnormality (Hydatidiform mole, Turner syndrome, etc.). Secondly, Villitis of Unknown Etiology (VUE). Thirdly, villus injury from mother's abnormal circulation. And fourthly, occlusive terminal villus capillary from cord occlusion or from occlusion of the vessels on the surface of the placenta.
In this paper I examine the pathological findings and clinical findings from cases of avascular villi over the period of one year, and classified those cases according to these four causes.
Material: I examined 122 singleton avascular villi cases. I classified each pathologically and studied the clinical findings.
Results: Pathologically, there were cases of dysmature villi, avascular villi of VUE, avascular villi from problems with the circulation from mother to placenta, and avascular villi due to bad fetal to placental circulation. I saw all four categories in the 122 cases.
Pathologically, out of 122 cases, I found:
19 cases of dysmature villi
15 cases of VUE
49 cases of avascular villi from bad circulation from mother to placenta
51 cases of coiling or abnormal insertion of cord
Clinically, from the 122 cases, I found:
15 cases of IUFD
16 cases of HDP
18 cases of GDM
24 cases of FGR
18 cases of NRFS (non-reassuring fetal status)
Conclusions: In avascular villi it is usual to expect IUFD, but I also found high rates of complications with HDP, GDM, FGR and NRFS. In this paper I study how widespread avascular villi is commonly associated with more sever perinatal problems.

S-01.
AMINO ACID TRANSPORTATION IN THE PLACENTA AND ITS IMPORTANCE IN FETAL GROWTH

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Objective: Insufficient oxygen supply is closely associated with the pathophysiology of fetal growth restriction (FGR). By using transgenic mice with its oxygen delivering capacity deteoriorated, we examined the phenotype of the mice and aimed to elucidate the underling mechanism by which the phenotype is induced.
Methods: Conditional knockout mice with erythrocyte-specific gene deletion of ENT1 (eEKO), a key adenosine transporter, were utilized in this study. The oxygen delivering capacity was measured by measuring p50 and 2,3-BPG in the erythrocytes. The dams were sacrificed on 17.5 dpc (days post coitus), and blood pressure, proteinuria, and the weight of the pups were measured. Metabolic profiling was used to determine the change of nutrient transports from the dam to the fetus by using maternal plasma and the placenta. We conducted real-time PCR, western blot, and in vivo experiment using human trophoblast cell line (HTR-8/SVneo cells) to access the molecular mechanism underlining the phenotype.
Results: eEKO showed reduction in oxygen delivering capacity in both p50 and 2,3-BPG in the maternal erythrocytes. The dams did not show hypertension or proteinuria, but they showed reduction in fetal weight, suggesting they have FGR phenotype. The immuno-staining in the placenta showed overexpression of HIF-1a in the placenta of eEKO, suggesting hypoxia in the placenta. Metabolomic profiling showed reduction of broad spectrum of amino acids in the placentas from eEKO, although the amino acids were rather increased in the maternal plasma, which implies the impaired amino acid transport function. Both real-time PCR and the western blot analysis showed reduction of LAT1, amino acid transporter, in the placentas from eEKO. Culturing HTR cells in HIF-1a stabilized state showed reduction of LAT1 in the placenta.
Conclusion: Our findings suggest that maternal erythrocytes'oxygen delivering capacity mediated by ENT1 is essential for maintaining adequate placental oxygenation to support fetal growth predominantly through LAT1. Strategies to improve erythrocytes' function to deliver oxygen may provide new therapeutic possibilities for FGR.

S-02.
RECOMBINANT HUMAN SOLUBLE THROMBOMODULIN AS AN ANTICOAGULATION THERAPY IMPROVES RECURRENT MISCARRIAGE AND FETAL GROWTH RESTRICTION DUE TO PLACENTAL INSUFFICIENCY

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Objective: Placental insufficiency is one of the major risk factors for growth restriction and preeclampsia. The purpose of this study is to investigate whether recombinant human thrombomodulin(r-TM) as anticoagulant therapy improves fetal conditions and physiological outcomes.
Methods: We used CBA/J×BALB/C mice as a control and CBA/J×DBA/2 mice — a well-studied model of recurrent spontaneous miscarriage. Pregnant mice received daily subcutaneous injections of r-TM or saline from day 0-15. The fetal resorption rate, fetal weight, and fetal size were calculated at day 15. Additionally, we analyzed the mRNA expression of angiogenic factors and the concentration of soluble Flt-1 (sFlt-1) using the ELISA kit.
Results: The rate of fetal resorption in CBA/J×DBA/2 mice treated with r-TM was significantly lower compared with mice without r-TM treatment. Additionally, fetal weight and fetal size were also significantly higher in the r-TM treated mice. Fibrinogen deposition in the labyrinth area of the CBA/J×DBA/2 mice treated with r-TM was significantly lower compared with deposits in the mice untreated with r-TM. As well, r-TM significantly increased the gene expression level of VEGF and Flt-1 mRNA in the placentas of the CBA/J×DBA/2 mice. r-TM treatment also significantly

decreased the production of sFlt-1 protein in the placentas of pre-eclampsia-like diseased mice.
Conclusion: r-TM as an anticoagulation therapy has the potential for the medical treatment of recurrent miscarriage and fetal growth restriction due to improved angiogenic factors. Additionally, r-TM treatment has the potential for the recovery of placental insufficiency and preeclampsia.

S-03.
THE PRODUCTION OF ANGIOGENIC AND ANTIANGIOGENIC FACTORS VIA THE ACTIVATION OF PROTEIN KINASE C IN THE PLACENTA UNDER HIGH-GLUCOSE CONDITIONS

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Objective: Abnormal glucose metabolism during pregnancies is a risk factor for preeclampsia (PE). Disruption of the balance between angiogenic and antiangiogenic factors is linked to PE pathogenesis. In high-glucose conditions such as a diabetes, a large amount of glucose incorporated into cells activate protein kinase C (PKC). The activation of PKC is intimately involved in the development of diabetic angiogenic complications and angiogenesis, and might be involved in the production of angiogenic and antiangiogenic factors in the placenta of pregnant women complicated with abnormal glucose metabolism. Therefore, we examined the production of angiogenic and antiangiogenic factors via the activation of PKC in the placenta under high-glucose conditions.
Methods: In the human trophoblast cell line HTR-8/SVneo cultured with high-glucose conditions, PKC activity was examined. Regarding angiogenic and antigenic factor, the mRNA expressions of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) were examined by real-time RT PCR. In pregnant diabetic mice (KK/TaJcl) and pregnant control mice (C57BL/6), placentas were removed on day 15 of gestation days, and blood were collected. PKC activity in placentas were compared between pregnant diabetic mice and pregnant control mice. Regarding angiogenic and antiangiogenic factors in plasma, sFlt-1 and PlGF were measured by ELISA and compared between pregnant diabetic mice and pregnant control mice.
Results: In high-glucose conditions, PKC activity was increased, and mRNA expressions of sFlt-1 and PlGF were also significantly increased. In placentas of pregnant diabetic mice, PKC activity was significantly increased. sFlt-1 was significantly increased in plasma of pregnant diabetic mice compared to pregnant control mice.
Conclusion: The activation of PKC might be involved in the production of angiogenic and antiangiogenic factors in the placenta under high-glucose conditions. These changes effect disruption of the balance between angiogenic and antiangiogenic factors, and might be involved in the development of PE in pregnant women complicated with abnormal glucose metabolism.

S-04.
AUTOPHAGY SUPPRESSION CAUSED BY ATG4B OVEREXPRESSION LEADS TO PREECLAMPSIA WITH FETAL GROWTH RESTRICTION

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Objective: Poor placentation is a common feature between fetal growth restriction without PE (FGR) and preeclampsia with FGR (PE w FGR). However, no one knows the differences between them in the pathophysiology. We aim to study the autophagy status in placental tissues.
Methods: Phosphorylated p62 (p-p62), an autophagy failure marker, and ATG4B, a protease that processes pro-LC3 paralogues, were immunostained in placental tissues obtained from normal pregnancies (NP), FGR, PE w/o FGR and PE w FGR. Two trophoblast cell lines, and human placental tissues were used.
Results: Bafilomycin A1, an autophagy inhibitor, increased p-p62 protein levels in placental tissues. Immunohistochemical analysis showed that the rate of p-p62 was significantly higher in PE w FGR than the other groups in EVT and syncytiotrophoblast cells, suggesting the autophagy inhibition in the PE w FGR placentas. To further clarify the mechanism of autophagy inhibition in PE w FGR, autophagy-related proteins were comprehensively compared among PE w FGR, FGR, and NP by western blot. Remarkable upregulation was seen in ATG4B as well as p-p62 in PE w FGR. Finally, overexpression of ATG4B introduced by adenovirus vector completely blocked the activation of autophagy in a dose-dependent manner in TCL1 cells.
Conclusion: ATG4B has been reported to contribute to the activation of autophagy so far. This study, however, newly found that overexpression of ATG4B led to autophagy suppression in human trophoblasts. In addition, autophagy was more inhibited in PE w FGR than FGR. For our future tusk, autophagy activation, by which ATG4B is downregulated in placental tissues, might develop a specific-treatment for PE w FGR.