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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 inter face 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 cotrol groups. *COL1A1* mRNA was decreased and *COX2* mRNA and PGE2 synthesis were increased by C. Prolifiration 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. Futhermore *COL1A1* mRNA levels was decreased by both HC and IL-1B.
Conclusion: GC weakens amnion via collagen degradation by MMP and supression of collagen synthesis. Induction of MMP and prostaglandin synthesis woud 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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Introduction: Feto-maternal tolerance is essential for pregnancy maintenance. Seminal priming induces temporal inflammation and immature uterine DCs that would be related to tolerogenic DCs at the time of implantation. Additionally seminal plasma has been proposed to contribute to tolerance. We clarified dynamic changes of uterine DC phenotype related to sperm and seminal plasma.
Materials & Methods: Female C57BL/6 mice were mated with male intact, seminal vesicle-excised (SVX), or vasectomized (VAS) BALB/c mice. Non-mated control mice were prepared in the estrous stage. Uterine DCs were analyzed at days 1.5 and 3.5 post-coitus (pc) by using the flow cytometry.
Results & Discussion: Uterine $CD45^+F4/80^-CD11c^+$DCs were classified into $CD103^-$DCs, $CD103^+$DCs, and PDCA-1^+plasmacytoid DCs (pDCs). In addition, those were subdivided into immature and mature DCs based on their expressions of CD86 and MHC class II. At day1.5 mature DCs in $CD103^-$DCs and $CD103^+$DCs were increased in intact and SVX, but not changed in VAS. At Day3.5 immature DCs were increased in each mating. Then the level of PD-L2 expression on mature DCs were upregulated than immature DCs before implantation.
Conclusion: Seminal plasma might contribute to tolerogenic condition without maturation of DCs. Before implantation it might be two types of uterine DCs. One is the immature DCs as it used to be proposed, the other is mature DCs expressing PD-L2 which contribute to induction of feto-maternal tolerance by inhibiting effector T cells.

9.
LNCRNA H19-DERIVED MIR-675-5P IS INVOLVED IN THE REGULATORY MECHANISM OF TROPHOBLAST INVASION

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Objective: MicroRNA *miR-675-5p* is generated from long non-coding RNA (lncRNA) *H19* that is highly expressed in human trophoblasts, especially extravillous trophoblasts (EVTs). However, the role of *miR-675-5p* in EVTs is not established. In this study, we investigated the effect of *miR-675-5p* on EVT invasion; moreover, we compared the expression levels of *miR-675-5p* between normal and preeclampsia (PE) placentae.
Methods: For evaluation of the effect of *miR-675-5p* on EVT invasion, *miR-675-5p* was overexpressed in the HTR-8/SVneo EVT cell line. Cell invasion ability and gene expression were evaluated by Matrigel-coated Transwell assay and real-time PCR, respectively. For analysis of *miR-675-5p* expression in the human placenta, placental samples were obtained from the pregnant women who gave informed consent (normal: $n = 10$, early onset PE: $n = 7$, late onset PE: $n = 4$). The expression levels of placental *miR-675-5p* were evaluated by real-time PCR.
Results: Regarding evaluation of the effect of *miR-675-5p* on EVT invasion, cell invasion was significantly activated in *miR-675-5p*-overexpressing HTR-8/SVneo cells. Cell invasion-related genes (e.g., *CXCL12*) were significantly upregulated in the cells. As to *miR-675-5p* expression in the human placenta, its expression was significantly upregulated in early onset PE placentae (1.82-fold median increase) and late onset PE placentae (1.73) as compared with normal placentae.
Conclusion: Our findings suggest that *miR-675-5p* accelerates EVT invasion. Aberrant expression of *miR-675-5p* might be involved in the pathogenesis of PE.

10.
DAMAGE OF AMNIOTIC EPITHELIUM BY DNA OXIDATIVE STRESS IN DIFFUSE CHORIOAMNIOTIC HEMOSIDEROSIS

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Introduction: The amniotic membrane plays an important role in the physiological maintenance and protection of the embryo. Dysfunction of the amniotic membrane is thought to have an adverse effect on the continuation of pregnancy. Diffuse chorioamniotic hemosiderosis (DCH) occurs when marginal or sub-chorionic placental hemorrhage migrates into the amniotic fluid and diffusely deposited as hemosiderin in the chorionic plate or membrane. Amniotic epithelial necrosis is frequently identified in DCH. In this report, we examined the pathological changes in the amniotic epithelium in three cases of diffuse chorioamniotic hemosiderosis (DCH) and investigated the relationship with DNA oxidative stress.
Result: DCH was confirmed by berlin blue staining, and amniotic necrosis was severe depending on the deposition of hemosiderosis. Immunostaining of 8-OHdG (8-hydroxy-2'- deoxyguanosine) which is a marker of DNA oxidative stress showed that presence of 8-OHdG in amniotic epithelium was positive in the amniotic epithelial cells.
Discussion: In this report, we describe two new findings: (i) the severity of DCH is related to amniotic epithelial necrosis, and (ii) the amniotic epithelium sustains oxidative stress in association with DCH. We speculated that oxidative DNA damage of the amniotic epithelium occurs by decomposition products of blood cells in cases of sub-chorionic hematomas and pathological DCH. Disorders of the amniotic epithelium may also disrupt the balance of the amniotic fluid volume and cause oligohydramnios.

11.
THE PREDICTION OF ABNORMALLY INVASIVE PLACENTA IN SUBSEQUENT PREGNANCIES AFTER UTERINE ARTERY EMBOLIZATION FOR POSTPARTUM HEMORRHAGE

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Objective: It has been reported that pregnant women with histories of uterine artery embolization (UAE) are at high risk for abnormally invasive placenta (AIP). The aim of this study was to evaluate the predictive accuracy of imaging examinations for AIP in subsequent pregnancies after UAE for postpartum hemorrhage (PPH).
Methods: This retrospective study enrolled 14 pregnant women with histories of UAE for PPH who underwent both ultrasonography (US) and magnetic resonance imaging (MRI) during subsequent pregnancies from 2011 to 2019. US finding of grade 3 placental lacunae, bridging vessels, and loss of clear zone were evaluated, in addition to MRI findings. The predictive accuracy was evaluated.
Result: Six of the 14 women (43%) were diagnosed as having AIP. In three of the 6 pregnant women (50%) with both histories of UAE and AIP, AIP could be predicted by imaging examinations, two by both US and MRI, and one by MRI alone. On the other hand, two of the eight pregnant women (25%) who had US or MRI findings suggestive of AIP didn't have AIP. The sensitivity, specificity, PPV, and NPV were 60%, 67%, 50%, and 75%, respectively.
Conclusion: The predictive accuracy of US and MRI examinations for AIP was not so high. In subsequent pregnancies after UAE for PPH, we must consider the risk of AIP despite the results of prenatal imaging examinations.

12.
CLINICAL CHARACTERISTICS OF DECIDUITIS IN THE PLACENTA AT THE TIME OF THE MID-TRIMESTER MISCARRIAGE AND PRETERM DELIVERY

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Objective: Patients who had a miscarriage or preterm delivery in the mid-trimester are often found with deciduitis associated with severe inflammation in the decidua. The aim of this study is to investigate the presence or absence of deciduitis and its clinical background in the mid-trimester miscarriage and preterm delivery cases.
Methods: The subjects were 37 patients who had a miscarriage or preterm delivery in the mid-trimester due to labor pains or amniorrhexis between