P2.48-N.
DOES ALTERED PLACENTAL MORPHOLOGY AND FUNCTION EXPLAIN INCREASED INCIDENCE OF POOR PREGNANCY OUTCOME IN ADVANCED MATERNAL AGE

Samantha Lean, Alex Heazell, Jane Boscolo-Ryan, Linda Peacock, Tracey Mills, Rebecca Jones *University of Manchester, Manchester, UK*

Objectives: Advanced maternal age (AMA; >35 years) is associated with an increased risk of fetal growth restriction (FGR) and stillbirth. Although their aetiology is unknown in this population, these pregnancy complications are linked to aberrant placental morphology and function and abnormal utero-placental and feto-placental blood flow. We hypothesised that placentas from AMA pregnancies have altered placental morphology and function.

Methods: Placentas were collected from singleton pregnancies of 20-30 (control), 35-39 and ≥40 year old women (n=15/group). Placental cell turnover was assessed by quantification of syncytial nuclear aggregates (SNAs) and proliferative index (Ki67 immunostaining). Placental nutrient transport was measured by uptake of ^{14}C-MeAIB and ^{3}H-Taurine via System A and TauT. Myometrial and chorionic plate artery (CPA) reactivity to U46619, bradykinin and sodium nitroprusside (SNP) was assessed by wire myography. Progesterone, human chorionic gonadotrophin and human placental lactogen were measured in maternal serum in third trimester by ELISA (n=25-29/group).
Results: The number of SNAs was increased in placentas from women aged 35-39 and ≥40 compared to controls ($p<0.05$). There was a trend towards reduced cytotrophoblast proliferation with increasing maternal age. Higher placental uptake via System A and TauT was detected in women ≥40 years compared to controls ($p<0.05$). CPAs from mothers aged 35-39 and ≥40 exhibited increased relaxation to SNP compared to controls ($p<0.001$), whilst constriction was augmented in myometrial arteries with AMA ($p<0.05$). Production of placental hormones was unaffected.
Conclusion: Increased SNAs may reflect accelerated placental ageing. Ageing is associated with inflammation and oxidative stress which increase system A and TauT activity in other tissues. Changes in placental and myometrial vascular function could also affect blood flow to the placenta and fetus in AMA pregnancies. These data provide evidence of placental dysfunction in AMA pregnancies which may explain the higher rates of stillbirth and FGR.

P2.49.
SFRP5 EXPRESSION IS REDUCED IN PLACENTAL JUNCTIONAL ZONE IN PREGNANT RATS FED A LOW PROTEIN DIET

Haijun Gao, Daren Tanchico, Uma Yallampalli, Chandra Yallampalli *Baylor College of Medicine, Houston, Texas, USA*

Our DNA microarray analyses on placental zones revealed that *Sfrp5* (secreted frizzled-related protein 5) was one of the down-regulated genes in pregnancy rats fed a low protein diet (LP). In this study we hypothesized that *Sfrp5* expression in placenta is reduced in LP rats, resulting in activated WNT signaling. Pregnant SD rats were fed a normal (control; CT) or LP from Day 3 until sacrificed at Days 14, 18 or 21 of gestation (n=8 rats/diet/day). Placental zones, junctional (JZ) and labyrinth (LZ) were collected. The mRNA levels of *Sfrp5*, *Wnt5a*, *Wnt11* (non-canonical WNT signaling stimulators), *Ctnnb1* (canonical WNT signaling mediator), *Atf2*, *Nfat5*, and *Jun* (transcription factors stimulated by non-canonical WNT signaling), *Ccnd1*, *Tcf7*, *Lef1* and *Wisp2* (transcription factors stimulated by canonical WNT signaling) in JZ and/or LZ were analysed by real-time PCR. Results include: 1) The mRNA levels of *Sfrp5* in JZ are about 10-fold higher than those in LZ; 2) The mRNA levels of *Sfrp5* in LZ were not affected in LP rats at all three days; 3) At Day 14, the mRNA levels of *Sfrp5* in JZ were not affected in LP rats; 4) In LP rats, the mRNA levels of *Sfrp5* were decreased ($P<0.01$) by 2.1- and 1.7- fold in female and male JZ at Day 18, respectively and by 1.9- and 2.8- fold in female and male JZ at Day 21, respectively. 5) Expressions of *Wnt5a*, *Wnt11, Nfat5*, *Jun, Ctnnb1, Ccnd1*, *Tcf7*, *Lef1* and *Wisp2* in JZ were not affected by LP at Day 18, while that of *Atf2* were increased by 1.5- ($P<0.05$) and 1.6- ($P<0.01$) fold in JZ in LP rats, respectively. In summary, *Sfrp5* expression in JZ is decreased in LP rats in late pregnancy, which may activate non-canonical WNT signaling targeting on *Atf2*.

P2.50.
PLACENTAL OXIDATIVE STRESS, SELENIUM AND PRE-ECLAMPSIA

Anthony Vincent, Alisha Khera, Jessica Vanderlielie *Griffith University, Southport, QLD, Australia*

There is considerable evidence that placental oxidative stress plays a significant role in the aetiology of preeclampsia. The current study addresses the role of endogenous anti-oxidant systems in preeclampsia. In particular, data on the selenodependent enzymes glutathione peroxidase and thioredoxin reductase will be presented and the role of selenium in preeclampsia will be considered. The aim of these studies was to determine the levels of endogenous antioxidants, selenium, and biological oxidation in normal and preeclamptic placental tissues. Furthermore, animal studies were conducted to assess the impact of selenium depletion on antioxidant expression and activity, oxidative stress and symptoms of preeclampsia. Selenium depletion generated placental oxidative stress and produced a preeclamptic like syndrome in pregnant rats suggesting a link between placental oxidative stress, endogenous antioxidant disequilibria and the pathogenesis of preeclampsia that may be linked to insufficient dietary selenium. The selenium status of preeclamptic mothers was also considered and lower levels of selenium were observed when compared to normal controls. Selenium supplementation improves endogenous antioxidant expression in trophoblast cells and improves mitochondrial respiration. Clinical studies are now underway to investigate the benefits of low dose selenium supplementation on the development and progression of preeclampsia. Selenium supplementation might provide an effective method of protecting the placenta from oxidative stress during preeclampsia.

P2.51.
IDENTIFICATION OF A NOVEL BIOMARKER RELIABLY PREDICTING THE RISK FOR SEVERE PREECLAMPSIA

Ming Liu [a], Yongqing Wang [b], Yangyu Zhao [b], Xuan Shao [a], Lei Ji [a], Yuxia Li [a], Christopher Redman [c], Jie Qiao [b], Yan-ling Wang [a] [a] *State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China;* [b] *Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing, China;* [c] *Nuffield Department of Obstetrics and Gynecology, Oxford University, Oxford, UK*

Objectives: Preeclampsia has been a leading cause of maternal and perinatal morbidity and mortality. One of the big challenges to minimize the adverse impact of preeclampsia is the identification of reliable and specific early-prediction biomarkers. In this present study, we aim to identify biomarkers in plasma of PE patients at the first half pregnancy.

Methods: Based on our previous results of data mining and proteomics, a group of soluble proteins were selected as candidates for further identification in a prospective cohort of 2954 nulliparous Chinese Han women. The plasma levels of these candidates from gestational week 6 through term were longitudinally measured among the normal pregnant women, severe preeclamptic and mild preeclamptic patients, as well as women with other pregnancy disorders. The relevance of the concentrations of these proteins to the risk of preeclampsia was statistically analyzed.
Results: Our data demonstrated that the circulating level of one candidate protein was significantly and consistently lower in severe preeclamptic patients than in normal pregnant women from gestational week 11 through term. Most notably, there was distinguishing difference in values of this protein between severe preeclamptic and normal pregnant women from weeks 15 to 26 (sensitivity 0.95, 95% CI 0.92-0.98; specificity 0.93, 95% CI 0.90-0.97). Decreased plasma level of this protein can specifically and accurately predict the risk for developing severe preeclampsia at least 10 weeks before the onset of the signs of the disorder. To our knowledge, the association of this protein to the risk for preeclampsia has not been demonstrated.

Conclusion: A novel biomarker to specifically and reliably predict the risk for severe preeclampsia is successfully identified. Further investigations in larger cohorts including populations of other ethnic/genetic backgrounds are necessary.

P2.52.
THERAPEUTIC EFFECT OF MATERNAL MOLECULAR HYDROGEN ADMINISTRATION IN A RAT MODEL OF PREECLAMPSIA

Takafumi Ushida, Yukio Mano, Tomomi Kotani *Nagoya university graduate school of medicine, Nagoya city, Japan*

Objective: Preeclampsia is a pregnancy-specific condition characterized by new-onset hypertension and proteinuria. It is also occasionally related to fetal growth restriction. Some studies suggest that placental oxidative stress plays an important role in the pathogenesis of preeclampsia. Recently, molecular hydrogen (H2) is reported to prevent a variety of diseases associated with oxidative stress in model systems and in human. Here, we studied the efficacy of H2 using a rat model of preeclampsia.

Methods: We used the well-established reduced utero-placental perfusion pressure (RUPP) model of placental ischemia-induced hypertension in rat that mimics features of preeclampsia. RUPP was performed on day 14 of pregnancy, clips were placed around the aorta below the renal arteries and on both the left and right uterine arcade at the ovarian artery. The sham group underwent laparotomy on day 14 of pregnancy without RUPP procedure. Hydrogen-saturated water (HW) was orally administered ad libitum from day 12 to 19 of pregnancy. On day 19, mean arterial pressure (MAP) was measured via carotid catheters, and then fetus and placenta were collected by cesarean section.
Results: MAP and urinary protein were significantly increased in the RUPP group compared with the sham group. HW treatment attenuated both MAP and urinary protein (sham 4.73, RUPP 8.14 and RUPP+HW 5.88mg/dL, respectively). RUPP fetuses and placentas were significantly smaller than those of sham group. In the RUPP+HW group, the decrease in fetal and placental weights was improved (fetal weight, sham 2.25, RUPP 1.79 and RUPP+HW 1.98g, respectively; placental weight, sham 0.417, 0.381 and 0.416g, respectively).
Conclusion: The prophylactic administration of HW significantly attenuated features of preeclampsia. Moreover, fetal growth was also improved. These results suggest that maternal administration of HW could have a potential benefit for the prevention of preeclampsia as a novel intra-uterine therapy.

P2.53.
PREECLAMPSIA IN PREGNANCIES WITH AND WITHOUT DIABETES; THE ASSOCIATIONS WITH PLACENTAL WEIGHT. A POPULATION STUDY OF 655 842 PREGNANCIES

Johanne Dypvik [a,b], Ellen Marie Strøm-Roum [a,b], Camilla Haavaldsen [a,b], Lars Johan Vatten [c], Anne Eskild [a,b] [a] *Department of Obstetrics and Gynecology, Akerhus University Hospital, Lørenskog, Norway;* [b] *Institute of Clinical Medicine, University of Oslo, Oslo, Norway;* [c] *Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway*

Objectives: To study whether placental weight in pregnancies with preeclampsia differs by maternal diabetes status?

Methods: The study comprised all singleton deliveries in Norway from 1999 through 2010 ($n = 655\,842$). Data were obtained from the Medical Birth Registry of Norway. We used z-scores of placental weight to adjust for differences in gestational age at delivery between pregnancies, and we studied the distributions of placental weight z-scores in deciles (tenths) in preeclamptic pregnancies with and without diabetes and in normotensive pregnancies with and without diabetes.
Results: In pregnancies with preeclampsia, the mean placental weight was much higher in diabetic pregnancies as compared to non-diabetic pregnancies. Thus, among pregnancies with preeclampsia, diabetic pregnancies were overrepresented in the highest decile of placental weight (28.8%) whereas preeclamptic pregnancies without diabetes were underrepresented in the highest decile of placental weight (9.8%). The enlargement of the placentas in preeclamptic pregnancies with diabetes was also pronounced in pregnancies with preterm delivery, and 30.1% were in the highest decile of placental weight as compared to 5.1% of the preeclamptic pregnancies without diabetes.
Conclusion: In pregnancies with preeclampsia, the placenta was large when the mother had concomitant diabetes, whereas in preeclamptic pregnancies without diabetes the placenta was small and smaller than in normotensive pregnancies. This finding suggests that the placental role in preeclampsia may differ by maternal diabetes status.

P2.54.
ALPHA-1 MICROGLOBULIN AS A POTENTIAL THERAPEUTIC CANDIDATE FOR THE TREATMENT OF PREECLAMPSIA

Lena Erlandsson [a], Ludivine Doridot [b], Aurélien Ducat [b], Johann Castille [c], Jean-Luc Vilotte [c], Lena Wester Rosenlöf [a], Magnus Gram [a], Bo Åkerström [a], Daniel Vaiman [b], Stefan Hansson [a] [a] *Institution for Clinical Sciences in Lund, Lund University, Department of Obstetrics and Gynecology, Lund, Sweden,;* [b] *INSERM U1016, Institute Cochin, Paris, France;* [c] *INRA UMR1313, Génétique Animale et Biologie Intégrative, Jouy-en-Josas, France*

Objectives: Preeclampsia (PE) is one of the most serious pregnancy-related diseases. Clinical manifestations, hypertension and proteinuria, appear after 20 gestational weeks. The worldwide prevalence is 3-7%, making it the most common cause of maternal and fetal mortality. PE lacks an effective therapy, and the only "cure" is delivery. We have previously shown that increased production and accumulation of free fetal hemoglobin (Hb) in the placenta is important in the pathophysiology of PE and that alpha-1-microglobulin (A1M) is involved in the defense against Hb, free heme and other oxidative species. In addition, exogenously administered A1M alleviates the effects of oxidative stress in the dual-placenta perfusion model and in pregnant ewes.

Methods: Most animal models mimic the symptoms of PE seen during later stages of the disease. In contrast, the STOX1 transgene mouse model develops symptoms based on a defect placenta, early in pregnancy, as well as the late classical symptoms. STOX1 is a transcription factor associated with PE that modulates proliferation and migration of trophoblasts. Wild type females are mated to STOX1-transgenic males, thereby restricting the transgene expression to the placenta.
Results: A1M was evaluated as a therapeutic agent to alleviate the symptoms observed in the STOX1 PE-model. Two groups of female mice were crossed with STOX1-transgenic males and developed PE symptoms. One group received A1M injections i.p. from day 6 of pregnancy, while the other group received buffer. Preliminary results demonstrate that A1M significantly reduced the hypertension during gestation, especially at mid-gestation. In addition, it significantly reduced proteinuria throughout pregnancy. A1M treatment had no significant effect on increased plasma levels of anti-angiogenic factors or the reduced litter size observed in the STOX1 PE-model. A1M was well tolerated with no side effects at the given dose.
Conclusion: A1M was able to alleviate the hypertension and proteinuria observed in the STOX1 PE-model.

P2.55.
FETAL HEMOGLOBIN INDUCES CHANGES TO THE GLOMERULAR FILTRATION RATE IN KIDNEY THAT RESEMBLES SYMPTOMS OBSERVED DURING PREECLAMPSIA AND WAS AMELIORATED BY CO-ADMINISTRATION OF ALPHA-1 MICROGLOBULIN.

Åsa Nääv [a], Lena Erlandsson [a], Josefin Axelsson [b], Irene Larsson [a], Martin Johansson [d], Lena Wester Rosenlöf [c], Isac Zia [a], Vera Casslén [a], Magnus Gram [c], Bo Åkerström [c], Stefan Hansson [a] [a] *Institution of Clinical Sciences in Lund, Lund University, Dep. of Obstetrics and Gynecology, Lund, Sweden;* [b] *Institution of Clinical Sciences in Lund, Lund University, Dep. of Nephrology, Lund, Sweden;* [c] *Institution of Clinical Sciences in Lund, Lund*