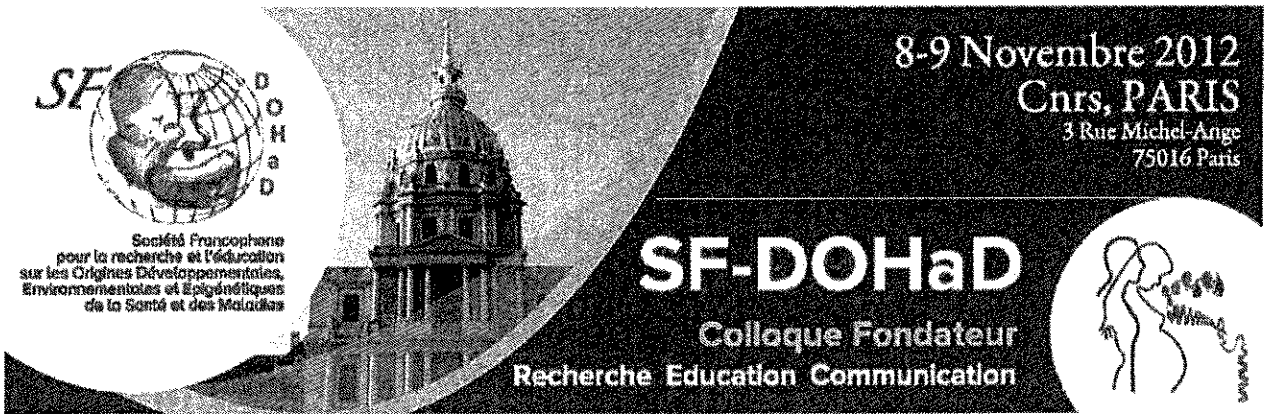
Maternal lipid and cholesterol-enriched diet disrupts fetal development and placental function in a rabbit model

Anne Couturier-Tarrade, Marie-Christine Aubrière, Olivier Morel, Nicole N. Charpentier, Michèle Dahirel, J. Bertrand-Michel, Pascale Chavatte-Palmer

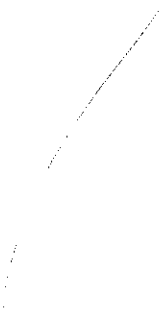


Journal of Developmental Origins of Health and Disease
Volume 4, Supplement 1, March 2013
Proceedings of the founding meeting of SF-DOHaD
8-9 November 2012
Paris, France

Guest Editors: Marie-Aline Charles, Isabelle Le Huerou-Luron and Claudine Junien

Publication of this supplement was supported by the Société Francophone pour la recherche et l'éducation sur les Origines Développementales, Environnementales et Epigénétiques de la Santé et des Maladies. Abstracts of oral and poster presentations from the founding meeting of SF-DOHaD included in this supplement have been assessed by the Scientific Committee. They were reviewed by Editor-in-Chief of the Journal prior to publication, and may be cited.

With the support of:



ORAL N°31

Evaluation of diabetes' effects on placental fetal macrophages

G. Sisino, T. Bouckenooghe, S. Aurientis, L. Storme and A. Vambergue

EA4489 'Environnement périnatal et croissance', Université Lille Nord de, France

Fetal placental macrophages defined as Hofbauer cells (HBCs) are localized in the stroma adjacent to trophoblast and capillaries.[1] Several functions have been addressed to HBCs: transportation of ions, stimulation or inhibition of the other mesenchymal cell's proliferation, remodeling of the extracellular matrix, production of angiogenic growth factors[2] and the release of cytokines and chemokines. Several studies focused on the link between HBCs and some pregnancy complications,[3] but nothing was reported about the role of HBCs in the placenta of women affected by maternal diabetes. Macrophages can respond to the hyperglycemic stimulation modifying their phenotypic profile switching from M2 (anti-inflammatory) to M1 (pro-inflammatory).[4] Notably, HBCs in a 'normal' placenta are identified as M2 macrophages. In the light of this background, our goal is to clarify the effect of 'diabetes' on placental fetal macrophages (i.e. HBCs) *in vitro* and *in vivo* (animal models). Our preliminary data demonstrated: (1) an imbalance at transcriptional level between some pro- and anti-inflammatory cytokines and some M1 and M2 markers in diabetic versus control rat placentas; (2) the purified HBCs cultured in high-glucose medium have showed an increase of some of the pro-inflammatory cytokines (Il12b, Tnfα) and a decrease of some anti-inflammatory cytokine (Il10, Il4) at mRNA level. Once we provide evidence that hyperglycemia can switch the fetal placental macrophages from M2 to M1's profile, we will investigate whether maternal hyperglycemia can program, at epigenetic level, the progeny's macrophages toward a pro-inflammatory profile, leading to a predisposition to metabolic diseases in adulthood. The results obtained in our animal model will be used as preliminary data to start the profiling of HBCs in type 1 and type 2 diabetic women's placentas (Cohort DIAMANT).

Key words: diabetes, fetal programming, immune function, placenta

Statement of interest: Authors report no conflict of interest.

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Email: giorgia.sisino@gmail.com

ORAL N°36

Maternal lipid and cholesterol-enriched diet disrupts fetal development and placental function in a rabbit model

A. Tarrade[1], M.-C. Aubrière[1], O. Morel[1], N. Charpentier[1], M. Dahirel[1], J. Bertrand-Michel[2] and P. Chavatte-Palmer[1]

[1]INRA-ENVA UMR1198 Developmental Biology and Reproduction, Jouy en Josas, ENVA, Maisons-Alfort, PremUp Foundation, Paris, France; [2]Inserm-Université Paul Sabatier UMR 1048-I2MC, Toulouse, France

We have shown that maternal administration of a lipid (8%) and cholesterol (0.2%)-enriched diet (HH diet) in a rabbit model leads to intrauterine growth factor (IUGR) and increased offspring susceptibility to excess body fat, overweight and hypertension in adults.[1] To examine the link between the fetal development and metabolic consequences in later life, placental development has been explored. Female rabbits were fed with a control (C) or HH diet from 10 weeks of age and throughout gestation. At 28 days of gestation, dams were anesthetized and a laparotomy was performed to collect placenta and plasma. Fetal weight in HH group was significantly reduced compared with C. Total cholesterol and triglycerides concentrations in HH fetuses were significantly increased by 1.2- and 2.3-fold, respectively, compared with C. The structural analysis of HH placentas revealed an abnormal accumulation of light vesicles, identified as lipid droplets in the trophoblast layer. Total content of cholesterol esters and triglycerides were also significantly increased in HH placentas. The expression of genes involved in placental growth, vascularization and nutrient transfer has been studied. HH placentas were characterized by a significant decrease in *LDL-receptor*, *CD36*, *LXR-α*, *ABC-G1*, *SLC38A1* and *SLC38A2* transcripts. The downregulation of *LXR-α* mRNA was correlated with a decrease in protein expression. These data demonstrate that maternal HH diet reduced cholesterol transport through the placenta as evidenced by placental gene expression and cholesterol ester accumulation. In contrast, fatty acid transport was not regulated, which could explain the excess of body fat in adults.

Key words: body composition, maternal diet, placenta, pregnancy, small animals

Statement of interest: Authors report no conflict of interest.

Reference

1. Picone O, *et al. Theriogenology.* 2011; 75, 287–299.

Email: anne.tarrade@jouy.inra.fr

ORAL N°54

Hyperlipidic hypercholesterolemic maternal diet affects early embryonic gene expression and trophoblast function

V. Duranthon, O. Picone, C. Archilla, N. Peynot, M. Dahirel, T. Aguirre-Lavin, N. Beaujean, A. Tarrade and P. Chavatte-Palmer

INRA UMR1198 Developmental Biology and Reproduction, Jouy en Josas, France; ENVA, Maisons Alfort, France; PremUp Foundation, Paris, France

Maternal diets have been shown to affect fetal development and postnatal health. However, their effects on early preimplantation embryo remain less documented. Feeding rabbit females with hyperlipidic (8%), hypercholesterolemic (0.2%) diet (HH diet) from 10 weeks of age resulted in intrauterine growth retardation of the progeny as soon as day 9 post fertilization.[1] We thus wondered whether early embryo was affected by this maternal diet. Therefore, we compared the transcriptome of embryos developed in HH-fed females with that of their control (C) counterparts at the stage just following the onset of embryonic genome activation (16–20 cell stage). Our transcriptome analyses evidenced the overexpression of ADIPOPHILIN in HH embryos. ADIPOPHILIN encodes for a protein involved in the early steps of lipid droplets formation from the endoplasmic reticulum. Its overexpression at embryonic genome activation stage was confirmed by quantitative RT-PCR analyses. It seems to be transient as transcript quantification at the blastocyst stage did not detect significant differences between HH and C embryos. However, very interestingly, immunocytochemical analysis of ADIPOPHILIN localization at the blastocyst stage showed that ADIPOPHILIN colocalized with Nile Red-stained lipid droplets in the cytoplasm of trophoblast cells in HH embryos. Such lipid droplets accumulation was not found in control embryos. Later on, during gestation, HH conceptuses displayed similar lipid droplets in the labyrinthine zone of their placenta, whereas C conceptuses did not. Thus, our results evidenced that embryo gene expression may be sensitive to maternal diet as early as embryonic genome activation stage, and gene deregulation may be involved in early perturbation of extraembryonic tissues that persists during pregnancy.

Key words: embryo, maternal diet, periods of plasticity, pregnancy, small animals

Statement of interest: Authors report no conflict of interest.

Reference

1. Picone O, *et al. Theriogenology.* 2011; 75, 287–299.

Email: veronique.duranthon@jouy.inra.fr

POSTER N°30

Transcriptomic analysis demonstrated a placental dysfunction during maternal diabetes

T. Bouckenooghe[1], P. Perimenis[1], E. Eury[2], S. Lobbens[2], G. Sisino[1], P. Gosset[3], J. Delplanque[2], P. Fontaine[4], L. Storme[1], P. Froguel[2] and A. Vambergue[1]

[1]EA4489 'Environnement périnatal et Croissance', Université Lille Nord de, France; [2]UMR 8199, Institut de Biologie de Lille, Lille, France; [3]Service d'Anatomo-pathologie GHICL, Lille, France; [4]Service d'Endocrinologie, CHRU Lille, Lille, France

Nowadays, there is increasing evidence for a role of the perinatal environment in the metabolic programming of adult life. A disturbed intrauterine milieu, such as maternal diabetes, can favorthe occurrence of chronic diseases in adulthood. In animal models of streptozotocin (STZ)-induced diabetes, few studies have assessed the potential role of the placenta and particularly the implication of feto-placental genes on fetal programming. In our work, we: (1) evaluate the consequences of maternal hyperglycemia on pups' metabolism; (2) use systems biology approach to analyzedifferentially expressed placental genes involved in intrauterine growth retardation (IUGR). We used three groups of animals: DS ($n = 5$, receiving 65 mg/kg of STZ at G7), D30 ($n = 9$, receiving sequentially STZ and 75 mg/kg of Nicotinamide at G7) and a control group ($n = 9$). We have evaluated metabolic parameters in mothers during gestation and in pups at birth. Placental whole-genome expression was performed to identify genes differentially expressed between experimental groups (Illumina). Diabetes in DS group is more pronounced than in D30 group. We have observed in our treated groups an IUGR with placental hypertrophy. Histological observations showed a clear hypovascularization. These observations have been correlated with our transcriptomic analyses showing a modification of genes implicated in angiogenic pathways. Especially, prolactin gene (Fold change >4) and protein were highly upregulated in the DS group partially explaining the hypovascularization that can be due to prolactin anti-angiogenic effect. We confirmed these observations in human on placental samples collected from patients with type 1 diabetes (DIAMANT Cohort). Maternal diabetes induces a profound modification of placental genes leading to a defect in angiogenesis. IUGR observed is the result of the placental hypovascularization and could profoundly modify the metabolic imprinting of the fetus.

Key words: developmental programming, diabetes, fetal programming, gestational diabetes

Statement of interest: Authors report no conflict of interest.

Email: thomas.bouckenooghe-3@univ-lille2.fr

POSTER N°32

Mild gestational hyperglycemia in rat induces fetal overgrowth and modulates placental growth factors and nutrient transporters expression

O. Cissé, I. Fajardy, A. Dickes-Coopman, E. Moitrot, V. Montel, E. Denhez, I. Dutriez-Casteloot, C. Breton, J. Lesage, D. Vieau and C. Laborie

EA4489, Unité Environnement Périnatal et Croissance, Université Lille Nord de France, France

Mild gestational hyperglycemia (MGH) constitutes an adverse environment during pregnancy and is often associated with fetal overgrowth.[1] Intrauterine environment is an important determinant for placental development, which is