measured a fetal and placental weight at embryonic day 18.5 and the epigenetic machinery genes expression in the placental labyrinth and fetal liver using RTq-PCR Taqman custom array card.

Results: At E18.5, OC fetuses presented intrauterine growth retardation (IUGR), while WL fetuses, despite maternal weight normalization before conception, showed a significantly decreased weight at term which was intermediate between OC and LC fetuses. Placental weight was not affected by maternal diet. Interestingly placenta was sexually dimorphic, with male placentas heavier than female ones. Expression of several epigenetic machinery genes was altered in OC placental labyrinths, especially for the genes implicated in the histone acetylation and deacetylation. In WL labyrinths the level of expression of some genes was restored to the LC level, while other genes showed similar profiles as in OC group.

Conclusions: Thus correction of maternal obesity by nutritional intervention in the preconceptional period only partially protects the offspring from IUGR. Further studies at the genome-wide level will elucidate the epigenetic targets and mechanisms of placental programming triggered by maternal ponderal trajectories.

YOUNG INVESTIGATOR SESSION.

YI 1.
MATERNAL SUPRAPHYSIOLOGICAL HYPERCOLESTEROLEMIA LEADS TO ENDOTHELIAL DYSFUNCTION OF THE HUMAN FETOPLACENTAL MACRO AND MICROVASCULATURE

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Maternal physiological hypercholesterolemia (MPH) occurs in pregnancy assuring fetal growth and development. However, maternal supraphysiological hypercholesterolemia (MSPH) leads to increased atherosclerosis in the fetal vasculature. In this study the maternal and neonatal total cholesterol (TCh) and lipoprotein levels were determined in a group of pregnant women and her newborns. A cut-off value for MSPH was established as maternal TCh levels at term of pregnancy >280 mg/dl. Pregnancies with values over this cut-off point were associated with fetoplacental endothelial dysfunction evaluated as reduced endothelial-dependent vascular dilation in the macro- (umbilical vein; 41 ± 7% and 10± 2% for MPH and MSPH, respectively) and microvasculature (veins in placental stem villi; 52 ± 6% and 1± 0.2% for MPH and MSPH, respectively). The mechanisms involved in this phenomenon include reduced nitric oxide synthase (NOS) activity and therefore reduced nitric oxide (NO) availability in human umbilical vein endothelial cells (HUVEC; reduction of 51 ± 2% compared with MPH) and human placental microvascular endothelial cells (HPMEC; reduction of 83 ± 4% compared with MPH). MSPH was also associated with reduced synthesis of the eNOS cofactor tetrahydrobiopterin (BH_4; reduction of 87.5 ± 5% compared with MPH) as well as increased activity of arginases, a group of enzymes that compete with NOS for the substrate L-arginine (1.5 times compared with MPH). Interestingly, the restoration of the BH_4 levels and the inhibition of arginases improved the endothelial function impaired by the MSPH condition. Therefore MSPH is a maternal condition likely involved in the endothelial dysfunction and the later development of atherosclerosis described for MSPH offspring. However, the mechanism(s) leading to the development MSPH as well as whether this maternal condition modifies the placental transport of cholesterol and therefore the fetal lipid function are actually unknown.

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YI 2.
PROGESTERONE AND ANANDAMIDE IN PREGNANCY LOSS

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It has been shown that abortion and changes in the endocannabinoid system (eCS) in peripheral lymphocytes of pregnant women are closely associated.

In a murine model of LPS-induced embryonic resorption (EmR), we studied the involvement of the eCS and infiltrating immune cells in the implantation sites, and its possible regulation by progesterone.

We observed an increase in the plasma levels anandamide (AEA), the most abundant endocannabinoid in the uterus. On the other hand, we found that LPS induced less EmR in cannabinoid receptor type 1 (CB1) knock-out mice, together with a lower increase in progesterone plasma levels. We demonstrated the presence of eCS in murine peripheral blood mononuclear cells (PBMC) and a higher activity of PBMC fatty acid amide hydrolase activity (FAAH) from pregnant mice when compared to non-pregnant mice. Moreover, we observed that progesterone, via its classical receptor (PR), had a protective effect on FAAH activity. Given that 70% of PBMC are T-lymphocytes, we demonstrated the presence of PR in this subpopulation.

During EmR, decidua is infiltrated with immune cells, suffers important damage and is finally expelled. Using a co-culture system, we investigated the effects of leukocyte infiltration on decidual FAAH activity. When deciduas from control mice were cultured in the presence of PBMC from LPS-treated animals, decidual FAAH activity was abolished. This effect was reversed by the co-administration of progesterone or aminoguanidine (a selective inhibitor of iNOS). When deciduas were co-cultured with PBMC from LPS treated mice, we observed an increase in decidual protein nitration, particularly in FAAH. This effect was reversed by progesterone treatment.

This work shows that eCS is involved in the LPS-induced EmR and that changes in the decidua are influenced both by infiltrating immune cells as well as by alterations in the endocrine system.

YI 3.
ROLE OF B CELLS IN PREGNANCY: LOOKING BEYOND ANTIBODY PRODUCTION

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The evolution of placental mammals has certainly represented a challenge to the already existing adaptive immune system. As a general rule, lymphocytes are immune educated during their development in order to recognize or "tolerate" self-antigens and only react against foreign ones. Failures in this crucial process of "learning" may lead to autoimmunity. However, during pregnancy in mammals, a clear exception of this immunological rule occurs. The maternal immune system has been adapted to temporarily accept the paternal, semi-allogeneic antigens carried by the fetuses, without losing the capacity to defend the mother against pathogens. This depends upon finely and highly regulated mechanisms involving both innate and adaptive immunity. In this regard, the role of different immune cells, including T cells, NK cells, and dendritic cells, has been extensively studied in pregnancy.