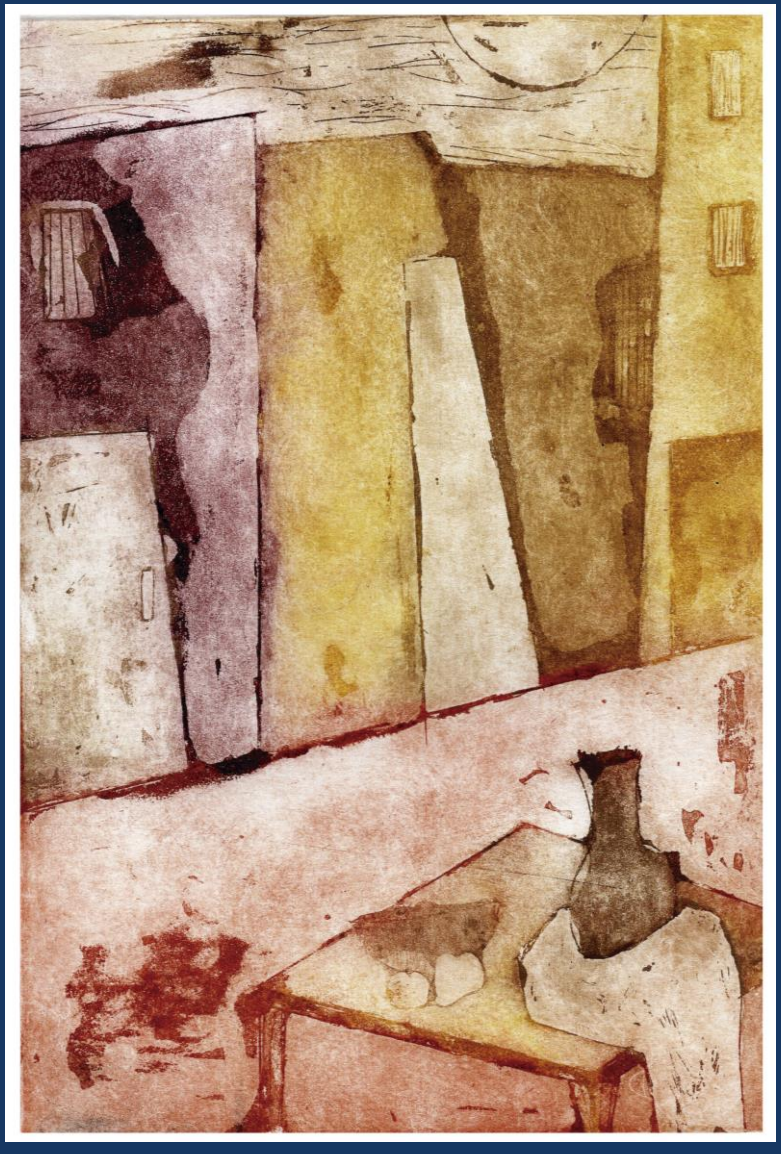
2019

# medicina

BUENOS AIRES VOL. 79 Supl. IV - 2019

## 80° Aniversario



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Volumen 79, Supl. IV, págs. 1-338

treatment, by RT-qPCR. To study IGF-1 and Notch pathway interaction we treated the MAC-T cells with 50 µM DAPT during 24, 48 and 72 h and 10 ng/ml IGF-1 during 24 or 48 h. We observed that IGF-1 reversed the decrease in cell viability induced by DAPT (72h DAPT-24h IGF-1). These results suggest that IGF-1 and Notch pathways may interact to regulate cell proliferation and migration in the bovine mammary cells. Further studies are needed to deepen the knowledge of the regulation of mammary gland development.

### 0960 - EFFECT OF PROTEIN RESTRICTION AND CONGENITAL VIRAL INFECTION IN BRAIN DEVELOPMENT DURING EMBRYONIC LIFE

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**U.E. ESTUDIOS EN NEUROCIENCIAS Y SISTEMAS COMPLEJOS, ENYS CONICET (1); UNIVERSIDADE FEDERAL DE RIO DE JANEIRO (2)**

**Abstract/Resumen:** During prenatal life, different environmental factors could affect normal brain development. It has been demonstrated that maternal malnutrition impacts on offspring neural development, although some authors have stated that brain growth is relatively preserved in comparison to other organs and tissues (brain sparing effect). As well, one of the consequences of maternal malnutrition is the impairment of the immunological condition, which could lead to more risk to be affected by different kinds of infections. Here, we evaluated the combined effect of maternal protein restriction and congenital Zika virus (ZIKV) infection in a mouse model. Wild-type mouse dams were exposed to a severe low-protein or a standard diet and they were infected with ZIKV during the peak of embryonic neurogenesis or exposed to a sham injection. Three days post-infection, dams were sacrificed and embryos were analyzed. Using immunohistochemistry labeling in brain embryos, we identified microglial cells (Iba1+) to assess the immune local response to viral infection in cases of nutritional deprivation. Also, proliferation processes in the ventricular and subventricular zone were analyzed using anti-ph3 antibody as a marker in order to infer if neurogenesis was affected by the interaction of protein restriction and ZIKV infection. We found that the embryos from dams that were undernourished and exposed to infection present abundant Iba1+ cells in the lateral ventricles, while this sign is absent in the other groups. Also, the quantification of ph3+ cells in this group revealed that there is a reduction of the dividing cells in the subventricular zone, while in the ventricular zone no significant differences were found ($p<0.05$). Our results highlight how protein restriction could enhance the effects of congenital ZIKV infection altering normal brain development, which has implications for human populations potentially affected by both factors.

## Reproducción/ Reproduction V

Chairs: Mónica Frungieri | Vanesa Hauk

### 0095 - MELATONIN AMELIORATES CHEMOTHERAPY-INDUCED OVARIAN DAMAGE

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**Abstract/Resumen:** Melatonin (MEL) is a lipofilic molecule which can act as a potent reactive oxigen species scavenger. MEL has been shown to protect tissues from severe oxidative stress. Premature ovarian failure (POF) is characterized by the depletion of ovarian follicles in young women, which may be caused by chemotherapy. Current treatments for POF, mainly hormone therapies, are not completely effective. One of the mechanisms underlying chemotherapy-induced POF is a strong increase in oxidative stress, which results in an aged ovarian phenotype. The present study proposes the application of MEL as a strategy to protect the ovary in patients undergoing chemotherapy. To induce POF, cyclophosphamide (CTX, 75mg/kg, i.p.) was applied in F1 mice (C57XBalbC 8 weeks old) on day 1. MEL (15 mg/kg, i.p.) was applied on days 1, 6 and 11. Sacrifices were made at day 15. The ovaries were isolated for histological analysis and protein extraction for Western blot assays. For all data analysis ANOVA followed by Tukey test were performed. An ovarian morphological analysis showed that CTX increased the % of primary and atretic follicles and reduced the % of antral follicles ($p<0.05$). MEL increased the % of antral follicles and decreased the % of atretic follicles compared to CTX ($p<0.05$). These results were corroborated by IHC for anti-Müllerian hormone (AMH), where it was found that CTX diminished the % of follicles expressing AMH, while MEL restored this value to control levels. CTX increased the BAX/BCL-2 ratio ($p<0.05$) while MEL restored this value to control levels. BAX/BCLX-L ratio remained unchanged. Given the antioxidant properties of MEL, the expression of catalase (CAT) and SOD1 were measured. CAT expression was unchanged, while SOD1 expression was reduced in CTX compared to control ($p<0.05$) but not in CTX+MEL compared to control. In conclusion, MEL administration might be a potential therapeutic agent for ovarian protection and fertility preservation in patients undergoing chemotherapy.

### 0157 - A MATERNAL DIET ENRICHED IN OLIVE OIL REGULATES MATRIX METALLOPROTEINASES ACTIVITY IN MATERNAL AND CORD BLOOD AND IN TERM PLACENTAS FROM WOMEN WITH GESTATIONAL DIABETES MELLITUS.

**Dalmiro GOMEZ RIBOT** (1) | Esteban DÍAZ(2) | María Victoria FAZIO(2) | Carlos GRESTA(2) | Valeria CAREAGA(3) | Marta MAIER(3) | Evangelina CAPOBIANCO(1) | Alicia JAWERBAUM(1)

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**Abstract/Resumen:** Matrix metalloproteinases (MMPs) are proteolytic enzymes involved in placental development, but markers of a pro-inflammatory state when produced in excess. Previous studies have established that gestational diabetes mellitus (GDM) induces a pro-inflammatory intrauterine environment. We hypothesized that a diet enriched in olive oil (OO) regulates MMP-2 and MMP-9 activities in placentas and in maternal and cord blood from women with GDM. Fifty control (C) and GDM women were enrolled after signing an informed consent (protocol approved by the Ethics Committee of Hospital Pirovano, Buenos Aires). All of them followed the WHO diet for pregnancy, and a group of GDM women received a 26 mL-OO addition daily from week 24-28 of gestation until delivery (GDMO group). At delivery, placental villous explants and maternal and cord blood were obtained and stored at -80ºC for zymography analysis. Fatty acids (FAs) profile was evaluated in cord blood by GC-FID. MMP-9 activity was increased in the placentas and in maternal blood of the GDM group (133 and 81 % respectively, $p<0.05$ vs. C), alterations prevented by the diet enriched in OO ($p<0.05$ vs. GDM). No changes were found in the MMP-2 activity among the three evaluated groups. Regarding cord blood, MMP-9 and MMP-2 activities were both increased in the GDM group compared to C (90 and 21 % respectively, $p<0.05$ vs. C), increases prevented by the OO addition ($p<0.05$ vs. GDM). These changes occurred without major changes in fatty acid composition in the cord blood from the three experimental groups. The diet enriched in OO modulates MMP-9 activity in term placentas and in maternal and cord blood, indicating the capability of this diet to module the pro-inflammatory intrauterine environment induced by GDM. The

lack of changes in FFA profile in cord blood suggest that the unsaturated fatty acids provided by the diet exert anti-inflammatory effects within the placenta and fetal organs, with possible benefits for the offspring's later life.

## 0174 - PATERNAL DIABETES INDUCED BY INTRAUTERINE PROGRAMMING AFFECTS LIPID METABOLISM IN THE PLACENTA

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**Abstract/Resumen:** Maternal diabetes programs diabetes in the adult offspring with alterations in peroxisome proliferator activated receptor (PPAR) pathways that regulate lipid metabolism. However, little is known about the paternal contribution to long-term offspring's metabolic health. The aim was to evaluate the regulation of lipid metabolism in the placenta of male fetuses from healthy pregnant rats that were mated with male diabetic rats. Control (C) and type 2 diabetic male rats (D, diabetes obtained by intrauterine programming, glycemia 140-190 mg/dL) were mated with control female rats. On day 21 of gestation, the pregnant and male rats were euthanized. The placenta, the fetuses and fetal plasma were obtained for evaluation. In paternal and fetal, the levels of plasma glycemia, triglyceridemia and cholesterolemia were evaluated by commercial kits. Lipid levels (by TLC) and mRNA levels of genes involved in lipid metabolism (by qPCR), were measured in the placenta of male fetuses from C and D rats. In the paternal plasma of D rats the levels of triglycerides and cholesterol were increased (39 and 21 %, respectively; $p<0.05$), as well as in fetal plasma of D group (39 and 21 %, respectively; $p<0.05$). Fetal weight was increased in D group (15 %; $p<0.05$), and placental weight was similar in both groups. The levels of triglycerides, cholesterol and free fatty acids were increased (46, 43 and 27, respectively; $p<0.05$) in the placenta of D group. The mRNA levels of PPARalpha and its co-activator PGC1alpha were increased in the placenta of D group (168 and 214 %, respectively; $p<0.001$). The mRNA levels of insulin-sensitive fatty acid transporter (FATP1) and endothelial lipase (LIPG) were also increased in the placenta of D group (95 and 106 %, respectively; $p<0.05$) when compared to C. Conclusion: Paternal diabetes induced by intrauterine programming leads to placental alterations in the lipid metabolism that could be related to the increase in the levels of lipids in fetal plasma. These metabolic alterations may lead to adverse consequences to the adult offspring.

## 0256 - REGULATION OF MTOR PATHWAY IN THE DECIDUA FROM DIABETIC RATS BY MATERNAL DIETS ENRICHED IN SUNFLOWER AND CHIA OIL DURING EARLY POSTIMPLANTATION

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**Abstract/Resumen:** Embryo development defects induced by maternal diabetes may start at early pregnancy when histotrophic nutrition occurs through the decidua. Leukine inhibitor factor (LIF) and insulin growth factor binding protein 1 (IGFBP1) participate in decidualization and development. Mammalian target of rapamycin (mTOR) pathway senses nutrient availability and is regulated by polyunsaturated fatty acids (PUFAs). The aims were to evaluate mTOR pathway, LIF and IGFBP1 gene expression in the decidua of diabetic rats at day 9 of pregnancy, and the effect of diets enriched in sunflower and chia oil (enriched in n-6 and n-3 PUFAs respectively) at early postimplantation on these parameters. Diabetes was induced by streptozotocin (50 mg/kg) in female Wistar rats 2 weeks before mating. On days 7, 8 and 9 of pregnancy diabetic rats received a standard diet or diets enriched in 6% of sunflower or chia oil. In the decidua of 9-days-pregnant rats mRNA levels of LIF, IGFBP1 and mTOR were measured by RT-qPCR and protein levels of 4EBP1, rpS6 and AKT (proteins downstream mTOR pathway) were measured by Western blot. The mRNA levels of LIF, IGFBP1 and mTOR were reduced in the decidua of diabetic rats ($p<0.001$, 71 %; $p<0.05$, 34 %; $p<0.05$, 54 %; respectively). PUFA-enriched diets prevented the reduced IGFBP1 mRNA levels and sunflower enriched diet also prevented the reduced LIF and IGFBP1 gene expression. Phosphorylated protein levels of 4EBP1, rpS6 and AKT were reduced in the diabetic group ($p<0.05$, 27 %; $p<0.05$, 40 %; $p<0.05$, 14 %; respectively), with no changes in total protein levels. PUFA-enriched diets restored the phosphorylated/total levels ratio of these proteins. Conclusion: the inhibition of the mTOR pathway and the low expression of LIF and IGFBP1 suggest impairments in decidualization and regulation of histotrophic nutrition at early postimplantation in diabetic rats. These alterations were prevented by PUFA-enriched diets suggesting benefits of these dietary treatments for early postimplantation development in maternal diabetes.

## 0312 - CYTOPROTECTIVE ROLE OF HUMANIN AGAINST OXIDATIVE STRESS IN GRANULOSA CELLS

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**Abstract/Resumen:** Humanin (HN) exerts a cytoprotective action in the presence of pro-oxidative agents in several tissues. Previously, we reported that inhibition of endogenous HN increases apoptosis in the human granulosa-like tumor cell line (KGN). Also, we demonstrated that HN decreases ROS production in KGN cells exposed to pro-oxidative environment. In the present study, our aim was to evaluate the anti-apoptotic action of HN, as a cytoprotective mechanism against oxidative stress in granulosa cells. To explore this aim, we assessed the percentage of TUNEL positive KGN cells incubated with HN (1 µM) for 30 min and $H_2O_2$ (150 µM) for further 1 h. Our results demonstrated that HN decreased the percentage of KGN TUNEL-positive cells induced by $H_2O_2$ (C: 0.3, HN: 0.7, $H_2O_2$: 2.1, $H_2O_2$+HN: 0.7, *$p<0.01$ vs respective control without $H_2O_2$, ^$p<0.01$ vs. respective control without HN; $X^2$ test). Also, we examined the effect of HN on apoptosis in granulosa cells from ovaries of prepuberal and adult rats incubated in pro-oxidative environment. Thus, we incubated each ovary from prepuberal or adult rats with HN (1 µM) for 30 min and $H_2O_2$ (150 µM) for further 1 or 2 h, respectively. Contralateral ovaries from rats of each treatment were used as respective controls. We determined the number of apoptotic granulosa cells per follicle by TUNEL. In prepuberal ovaries, we observed that HN decreased the number of apoptotic granulosa cells per follicle induced by $H_2O_2$ (C: 2.5 vs. HN: 4.0 ns.; C: 1.6 vs $H_2O_2$: 7.0 $p<0.05$; $H_2O_2$: 9.9 vs. $H_2O_2$+HN: 6.5 $p= 0.075$. paired t test). In adult rats, HN seemed to decrease the number of apoptotic granulosa cells per follicle induced by $H_2O_2$ (C: 6.2; HN: 9.0; $H_2O_2$: 34.8; $H_2O_2$+HN: 18.3). To conclude, our results suggest that HN protects granulose cells against oxidative stress, at least in part, through an anti-apoptotic mechanism.

## 0390 - MATERNAL ADMINISTRATION OF SODIUM BUTYRATE PREVENTS MACROSOMIA AND LIVER LIPID OVERACCUMULATION IN FETUSES FROM OBESE RATS