PRENATAL METFORMIN TREATMENT PREVENTS ESTRADIOL INCREASE AND PARTIALLY IMPROVES OVARIAN FUNCTION IN OFFSPRING OF OBESE MOTHERS

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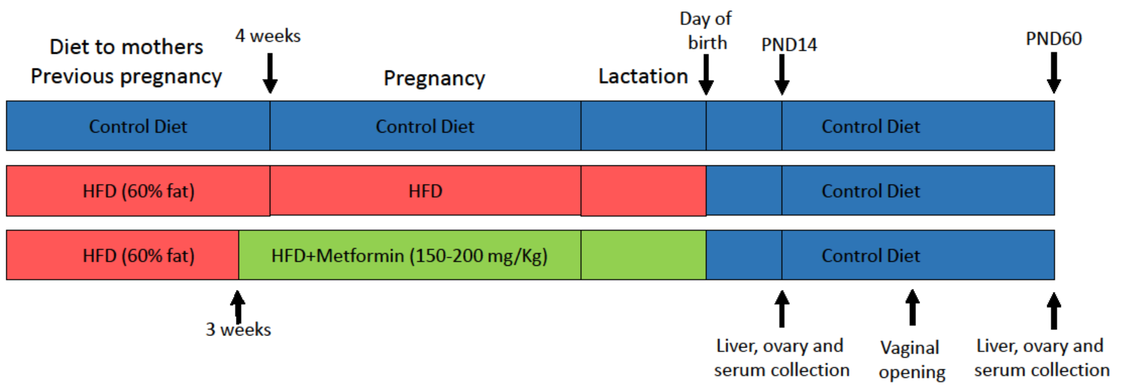
Abstract

Obesity epidemic is one of the major concerns in the world. Worryingly, a high percentage of pregnant women have obesity, which could imply several consequences. Maternal obesity leads to different abnormalities in pregnancy and delivery. In addition, recent studies show that the offspring of obese mothers has an increased probability to suffer cardiovascular, metabolic and reproductive diseases. We have previously demonstrated that exposure to a high fat diet is related to obesity, liver dysfunction, increased serum estradiol, advanced puberty and ovarian follicular alterations in the progeny. We aimed to determine if metformin prevents this developmental reprogramming produced by a high fat diet exposure. Our results shows that metformin did not affect the weight gain during pregnancy and failed in prevent increased weight in offspring of obese mothers. At PND14 metformin tended to prevent the estradiol increase while at PND60 metformin significantly prevented the estradiol increase. Coherently, hepatic CYP3A2 (enzyme that metabolizes estradiol) decreased in offspring obese mothers and this decrease was prevented by metformin treatment. The generation of ovarian cyst was also prevented by metformin in offspring of obese mothers. In conclusion, metformin prevented some reproductive alterations triggered by maternal obesity on the offspring.

Methods



Results

1.- Metformin fails in prevent the increase in body weight in offspring of obese mothers, and does not change the maternal weight during pregnancy.

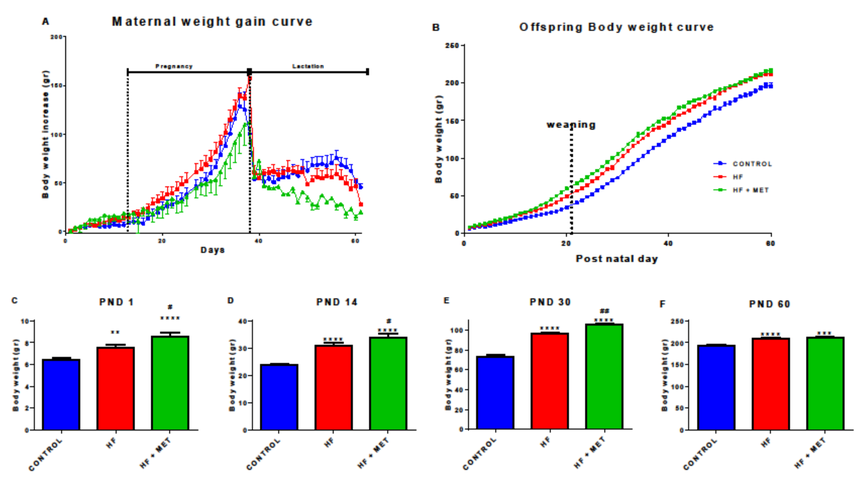


Figure 1.- Body weight PND 1- 60. A) Body weight gain of mother during pregnancy and lactation (n: C=7, HF=5, HF+MET=4) B) Body weight of the offspring from the PND 1 to 60 (n: C = 37; HF = 31; HF + MET = 14) C) PND 1 (HF = 31 HF + MET = 14 C = 37 n) E) PND 30 (n: C = 28; HF = 24; HF + MET = 10) and F) PND60 (n: C = 25; HF = 22; HF + MET = 9). Results are expressed as the mean + SEM. * Compares the HF and HF + MET groups compared to the control, while # HF and HF + compares MET entity. # P <0.05; ## P <0.01; ** P <0.01; *** P <0.001; **** P <0.0001.

2.- Metformin fails in prevent the advance puberty onset in offspring of obese mothers.

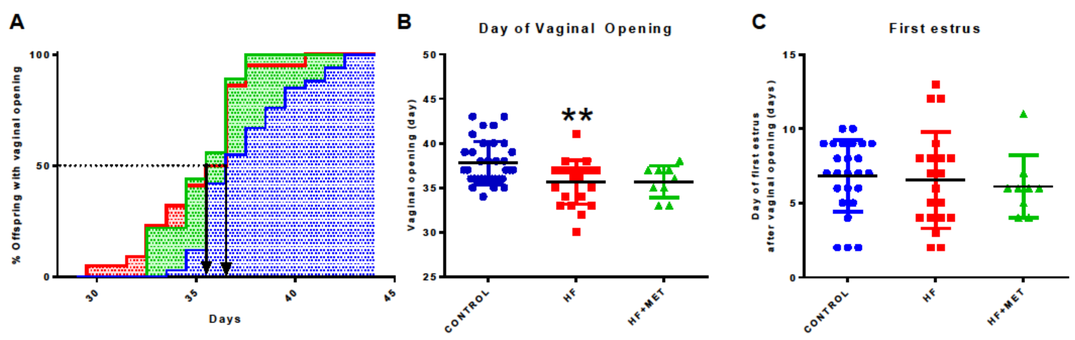


Figure 2.- Vaginal opening. A) The graph shows the percentage of rats that presents vaginal opening in HF and HF + MET groups B) The graph shows the dispersion of data for monitoring vaginal opening in the groups of A C) number of days to 1° oestrous after vaginal opening. (n: C = 34; HF = 22; HF + MET = 9). ** P <0.01

3.- Metformin prevents the estradiol increase in offspring of obese dams.

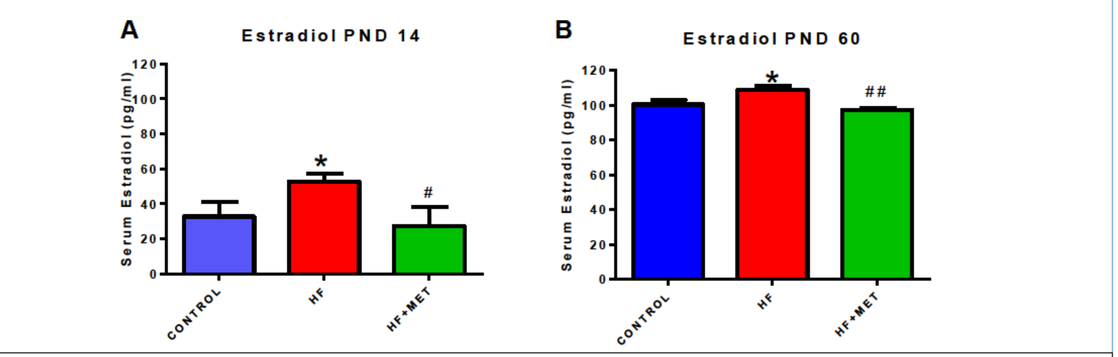


Figure 3.- Serum estradiol. A) Estradiol levels at PND14 (n: C = 4; HF = 4; HF + MET = 4), B)Estradiol levels PND 60. (n: C = 6; HF = 7; HF + MET = 5). * or # P <0.05, ## p <0.01. Mean± SEM. * Compares the HF groups compared to the control and # compares the HF+MET group with HF group.

4.- Metformin prevents the decrease in hepatic CYP3A2 in offspring of obese dams.

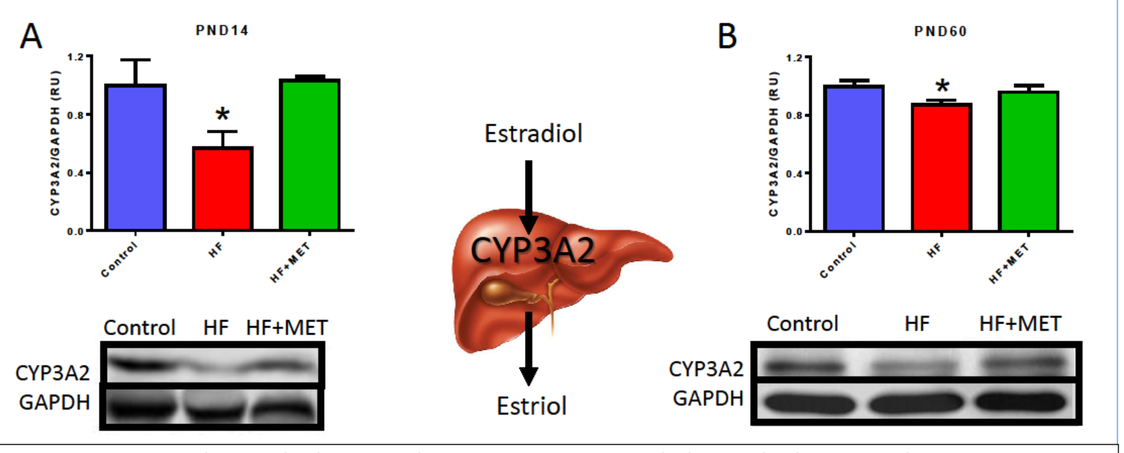


Figure 4.- Hepatic CYP3A2. A) CYP3A2 levels at PND14 (n: C = 5; HF = 5; HF + MET = 4), B)CYP3A2 levels at PND 60. (n: C = 5; HF = 6; HF + MET = 6). * P <0.05. Graph are plot as mean± SEM. * Compares the HF groups compared to the control. Each sample was measure 3 times. CYP3A2 levels were normalized with GAPDH.

4.- Metformin prevents the increase of follicular cysts in offspring of obese dams.

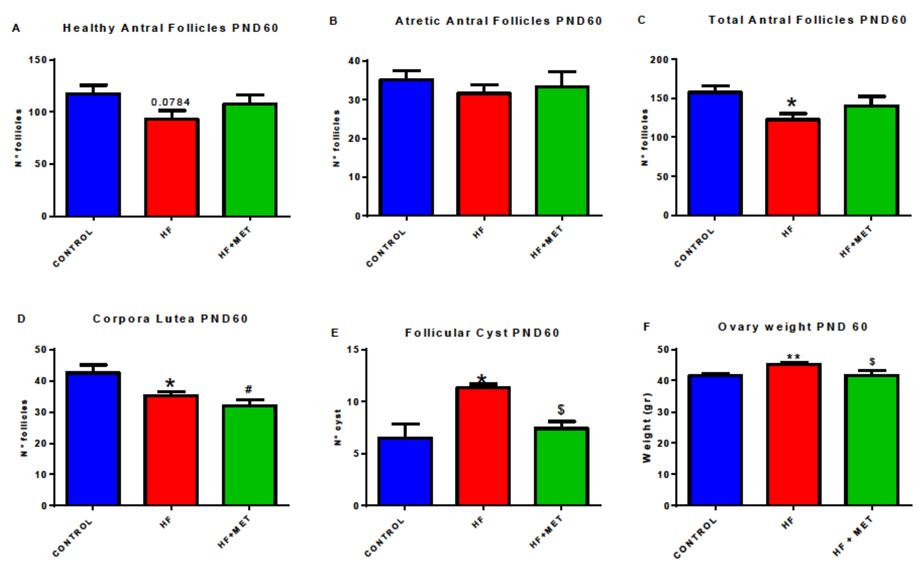


Figure 5.- Ovarian morphology at PND 60. A) Number of healthy antral follicles (n: C = 4; HF = 4; HF + MET = 5). B) Number of atretic antral follicles (n: C = 4; HF = 5; HF + MET = 5). D) Number of corpora lutea (n: C = 4; HF = 4; HF + MET = 4). E) Number of follicular cysts (n: C = 4; HF = 3; HF + MET = 5) and F) ovary weigth (n: Control=13, HF=9 and HF+MET=5) Results are expressed as the mean + SEM. * P <0.05, # p <0.05. * represents control versus HF, # represents HF versus control and $ represents HF versos HF+MET.

Conclusions

- Maternal metformin did not prevent the increase in body weigh in offspring of obese mothers
- Maternal metformin decreased estradiol levels and increase CYP3A2 levels in offspring of obese dams
- Maternal metformin prevented some reproductive alterations triggered by maternal obesity on the offspring.

This work was supported by Fondecyt Initiation Grant 11130707-CONICYT, Chile

ECE 2016, Munich, Germany