Prenatal Metformin Treatment Prevents Estradiol Increase and Partially Improves Ovarian Function in Offspring of Obese Mothers

Daniela Álvarez1, Sofia Olguin1, Karina Ceballos1, Jonathan Martinez2, Daniela Fernandois1,3, Ramón Sotomayor2 and Gonzalo Cruz2

1. Laboratorio de Alteraciones Reproductivas y metabólicas. CNPC, Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, 2360102, Chile. (gonzalo.cruz@uv.cl).
2. Laboratorio de Neuroquímica y Neurofarmacología, Centro de Neurobiología y Plásticidad Cerebral (CNPC), Instituto de Fisiología, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, 2360102, Chile.
3. Programa de doctorado en Farmacología, Facultad de Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile.

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 programming 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 cysts 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

Diet to mothers Previous pregnancy

<table>
<thead>
<tr>
<th>Control Diet</th>
<th>Control Diet</th>
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<tbody>
<tr>
<td>5% (50 kcal)</td>
<td>5% (50 kcal)</td>
</tr>
<tr>
<td>HF (50 kcal)</td>
<td>HF (50 kcal)</td>
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Pregnancy Day of birth Postnatal

<table>
<thead>
<tr>
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<tr>
<td>Estradiol PND 14</td>
<td>Estradiol PND 60</td>
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Lactation

<table>
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<th>Control Diet</th>
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<tr>
<td>Estradiol PND 180</td>
<td>Estradiol PND 180</td>
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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.

![Image of body weight graph]

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

![Image of vaginal opening graph]

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

![Image of estradiol levels graph]

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

![Image of hepatic CYP3A2 graph]

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

![Image of follicular cysts graph]

Conclusions

- Maternal metformin did not prevent the increase in body weight 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.

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