**RESULTS:**

Offspring of mothers (-13%) and of lipidic and glucidic metabolisms. Diet change induced statistics: p<0.05 for 1.0

<table>
<thead>
<tr>
<th>E18.5 foetal weight</th>
<th>CTRL</th>
<th>OB</th>
<th>WL</th>
</tr>
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<tbody>
<tr>
<td>0.1</td>
<td>15</td>
<td>35</td>
<td>ns</td>
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</table>

Non significance (ns) WL vs OB, a c WL vs CTRL, (mainly histone acetylation) -13% effects on offspring stress response and glucose metabolism [16-17].

In our model, it is unclear whether the decrease in foetal weight in response to environmental insults. The link between histone modifications and metabolic diseases is well established [18-21].

**Offspring long-term outcomes**

We tracked metabolic and behavioral outcomes of offspring born to CTRL, OB, WL mothers. After weaning, the offspring were either put on a CD or a HFD. The offspring were diet measured the vast majority of the metabolic and offspring outcomes. After only few weeks of HFD, the offspring developed obesity, metabolic alterations and offspring impairments, independently of maternal context.

**Deciphering epigenetic mechanisms in DOHaD.**

Most of the research projects studying the effect of maternal obesity focus on DNA methylation. However, our results, as well as other publications, point out that the N6-methylation (aldehyde) can be a key component [18-21]. This highlights the importance of investigating the mechanisms of regulation of histone marks in response to environmental stimuli. The link between histone modifications, metabolic states, and placental and hepatic function should be established.

**Obesity induced foetal growth restriction, transcriptional changes and worsen diet-induced obesity in adulthood. Maternal weight loss is beneficial with some possible adverse outcomes.**

**Conclusions, discussion and future prospects:**

Maternal obesity is associated with fetal growth restriction (13%) and increased proportion of small for gestational age fetuses (odd ratio 1.3-2). Maternal preconceptional weight loss lead to a complete normalisation of the foetal growth phenotype.

**Maternal phenotype**

Maternal obesity is associated with a wide range of fertility troubles, obstetrical and genital complications [1]. The babies are also at risk for stillbirth, growth phenotype (small or large birthweight), congenital malformations [2-4]. Moreover, according to the metabolic species of health and disease concept, maternal obesity predisposes the offspring to adult onset non-communicable diseases [5].

A preconceptional weight loss is widely recommended to obese women. However, its long-term outcomes on the offspring has been poorly assessed.

In human cohorts, it may have positive or negative effects on fetal growth [6-11]. Interestingly, none of these studies followed up the metabolic development of these children and adolescents and additional studies are therefore needed to reveal the long-term health profiles of offspring born to obese mothers who lost weight prior to conception [12-13]. In animal, preconception weight loss has been assessed in rodents, sheep and non human primates (macaque). In two rat models, a nutritional intervention in obese dams was beneficial to their offspring born to lean mothers. The babies are also at risk for stillbirth, growth phenotype (small or large birthweight), congenital malformations [2-4]. Moreover, growth [6-11]. Interestingly, none of these studies followed up the metabolic development of these children and adolescents and additional studies are therefore needed to reveal the long-term health profiles of offspring born to obese mothers who lost weight prior to conception [12-13].

**Foetal gene expression**

The expression of 60 epigenetic machinery genes and 32 metabolic genes was measured in the fetal liver, placental and, uterine junctional zone by RT-qPCR using TaqMan Low Density Arrays.

23 genes were affected by maternal weight trajectories in at least one of three tissues. The fetal liver and placental layers were more responsive to maternal obesity than placental zone. One third (18/58) of the epigenetic machinery genes were differentially expressed between at least two maternal groups. Genes involved in the Histone acetylation pathway were particularly altered (13/18).

In OB group, while most HDacs were downregulated, Atz1 and Atz2 were upregulated in WL group, the expression of only one subset of these genes was normalised.

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