Title: Ovarian stimulation perturbs methylation status of placental imprinting genes and reduces blood pressure in the second generation offspring

Authors: Gu-Feng Xu, Yun Liao, Jing-Yi Li, Yi-Feng Liu, Yun Huang, Yi-Qing Wu, Juan Liu, Ping-Ping Lv, Run-Jv Zhang, Dan Zhang

PII: S0301-2115(17)30094-5
DOI: http://dx.doi.org/doi:10.1016/j.ejogrb.2017.02.022
Reference: EURO 9795

To appear in: *EURO*

Received date: 5-11-2016
Revised date: 3-2-2017
Accepted date: 17-2-2017

Please cite this article as: Xu Gu-Feng, Liao Yun, Li Jing-Yi, Liu Yi-Feng, Huang Yun, Wu Yi-Qing, Liu Juan, Lv Ping-Ping, Zhang Run-Jv, Dan Zhang.Ovarian stimulation perturbs methylation status of placental imprinting genes and reduces blood pressure in the second generation offspring.*European Journal of Obstetrics and Gynecology and Reproductive Biology* http://dx.doi.org/10.1016/j.ejogrb.2017.02.022

Ovarian stimulation perturbs methylation status of placental imprinting genes and reduces blood pressure in the second generation offspring

Gu-Feng Xu[1,2#], Yun Liao[1#], Jing-Yi Li[1,2], Yi-Feng Liu[1,2], Yun Huang[1,2], Yi-Qing Wu[1] , Juan Liu[1,2], Ping-Ping Lv[1,2], Run-Jv Zhang[1,2], Dan Zhang[1,2]

[1]Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China
[2]Key Laboratory of Reproductive Genetics, Ministry of Education (Zhejiang University), Hangzhou, China

Correspondence

Address all correspondence and requests for reprints to: Dan Zhang, Ph.D., M.D, Department of Reproductive Endocrinology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China. Address: 1 Xueshi Road, Hangzhou, Zhejiang 310006, China; Tel: 0086-571-87061501; Fax: 0086-571-87061878; Email: zhangdan@zju.edu.cn.
# These two authors are considered similar in author order.

Abstract

Objective(s) Assisted reproductive technology (ART) is associated with DNA methylation dysfunction of offspring. However, it is unclear whether ovarian stimulation (OS) is responsible for DNA methylation dysfunction of offspring.
Study Design We built the first-generation (F1) and second-generation (F2) offspring mice model of ovarian stimulation. Bodyweight of F1 and F2 were measured. Expression levels of several imprinted genes (*Impact, H19, Igf2, Plagl1, Mest,* and *Snrpn*) in F1 placenta were tested. Methylation status of *Plagl1* and *H19* promoters was examined with bisulfite sequencing. Glucose tolerance, blood pressure, and heart rate were evaluated in F2 mice.
Results The OS F1 showed elevated bodyweights in the 2nd, 3rd and 4th weeks, but the difference disappeared in the 5th week. *Plagl1* was down-regulated in OS F1. Promoters of *Plagl1* and *H19* were also hypermethylated in OS F1. F2 of OS mice had the similar bodyweight and glucose tolerance compared with the control F2. However, F2 of OS ♂F1 + OS♀ F1 showed the decreased systolic pressure, diastolic pressure, and heart rate.