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Dietary caloric normalization or restriction as preconception care strategies: impact on metabolic health and fertility in high fat-induced obese outbred mice.

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Maternal metabolic disorders like obesity and metabolic syndrome are linked to decreased oocyte and embryo quality and thus reproductive failure. Overweight and obese patients are advised to lose weight before conception to increase the chance of a healthy pregnancy. Human studies show conflicting results and are often underpowered leading to a lack of scientifically substantiated advice. Furthermore, the effects of significant weight loss, due to caloric restriction, on oocyte quality are not known. Therefore, we aimed to feed a normal control or low calorie diet as preconception care strategy in high fat-fed obese Swiss mice to improve their metabolic health and oocyte quality. Five week old female outbred Swiss mice (as a model for human physiology) were fed a control (CTRL; 10% fat) or a high fat (HF; 60% fat) diet for seven weeks. Afterwards, HF-mice were switched to different preconception care interventions (PCCI) for six weeks, resulting in four treatment groups: 1) control diet for 13w (CTRL_CTRL), 2) high fat diet for 13w (HF_HF), 3) switch from a HF to an *ad libitum* CTRL diet (HF_CTRL) and 4) switch to a 30% caloric restriction diet (HF_CR). Change in body weight (n=156 mice, twice a week), metabolic health (glucose and insulin tolerance tests; n=32 mice), oocyte quality and pregnancy rates (n=32 mice) were studied. To assess oocyte quality, mature oocytes were collected after hormonal stimulation (10IU eCG followed by 10IU hCG 48h later, IP. injected) to evaluate oocyte's lipid content (Bodipy staining; 11-12 oocytes/group) and to examine mitochondrial ultrastructure by transmission electron microscopy (TEM; 4-5 oocytes/group). All data were analyzed using ANOVA and Bonferroni corrected. In comparison with the CTRL group, HF diet increased body weight after seven weeks (40.01±0.54g *vs.* 32.01±0.47g; $P<0.05$). After two weeks of PCCI, both HF_CTRL and HF_CR mice had lost weight, reaching similar weights as control mice. Overall, the deteriorated glucose tolerance and insulin sensitivity in the HF_HF group were normalized to levels similar to the CTRL_CTRL group in both PCCI. TEM of HF_HF-oocytes showed higher proportions of mitochondrial ultrastructural abnormalities, e.g. low electron density and rose petal appearance (Boudoures et al. (2016) Reprod, 151(3):261-70) compared to CTRL_CTRL (54.70% *vs.* 30.52%; $P<0.05$). After six weeks of PCCI, the proportions of mitochondrial abnormalities were partially reduced in both HF_CTRL (39.64%) and HF_CR (44.47%) groups. HF_HF diet increased the intracellular lipid content in oocytes with 84.41% compared to the CTRL_CTRL group ($P<0.05$). However, both PCCI strategies failed to alleviate this effect. HF_HF-fed mice displayed lower pregnancy rates compared to those on the CTRL_CTRL diet (12.5% *vs.* 100%; $P<0.05$). Pregnancy rates were completely restored in the HF_CTRL and HF_CR group. In conclusion, both PCCI improved metabolic health (reduced weight, restored glucose tolerance and insulin sensitivity), partially improved oocyte quality and restored pregnancy rates in HF-induced obese mice.